NIH AIDS Research Program Evaluation

VACCINE RESEARCH & DEVELOPMENT AREA REVIEW PANEL

Findings and Recommendations

Panel Members

Dani P. Bolognesi, Ph.D., *Chair*
Duke University Medical School
Bonnie J. Mathieson, Ph.D., *Executive Secretary*
Office of AIDS Research, NIH

Abul K. Abbas, M.D.
Harvard Medical School
Lawrence Corey, M.D.
University of Washington
Ronald C. Desrosiers, Ph.D.
New England Primate Research Center
Ellen Heber-Katz, Ph.D.
Wistar Institute
Maurice R. Hilleman, Ph.D., D.Sc.
Merck Institute for Therapeutic Research
Merck Research Laboratories
Jiri Mestecky, M.D.
University of Alabama, Birmingham
John Moore, Ph.D.
Aaron Diamond AIDS Research Center
James Mullins, Ph.D.
University of Washington
Harriet L. Robinson, Ph.D.
University of Massachusetts Medical Center
William Snow
ACT UP/Golden Gate
Kathelyn S. Steimer, Ph.D.
Biocine Corporation
Ralph Steinman, M.D.
Rockefeller University
Cladd Stevens, M.D., M.P.H.
New York Blood Center
Peter F. Wright, M.D.
Vanderbilt University Medical Center

Subpanel Members

Dani P. Bolognesi, Ph.D., ***Panel Chair***
Duke University Medical School

Basic Research Subpanel
John Moore, Ph.D., ***Chair***
Aaron Diamond AIDS Research Center
Abul K. Abbas, M.D.
Harvard Medical School
Lawrence Corey, M.D.
University of Washington
James Mullins, Ph.D.
University of Washington

Targeted Research Subpanel
Harriet L. Robinson, Ph.D. ***Chair***
University of Massachusetts Medical Center
Ronald C. Desrosiers, Ph.D.
New England Primate Research Center
Ellen Heber-Katz, Ph.D.
Wistar Institute
Maurice R. Hilleman, Ph.D., D.Sc.
Merck Institute for Therapeutic Research
Merck Research Laboratories
Jiri Mestecky, M.D.
University of Alabama, Birmingham

Clinical Trials Subpanel
William Snow, ***Chair***
ACT UP/Golden Gate
Kathelyn S. Steimer, Ph.D.
Biocine Corporation
Ralph Steinman, M.D.
Rockefeller University
Cladd Stevens, M.D., M.P.H.
New York Blood Center
Peter F. Wright, M.D.
Vanderbilt University Medical Center

OAR Staff

Bonnie J. Mathieson, Ph.D., ***Executive Secretary***
Elise DiSciullo, ***Program Assistant***

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Executive Summary

The development and application of an effective vaccine against HIV is our best hope for stemming the devastating consequences of the AIDS pandemic. This is particularly true because HIV infection has caused enormous social and economic losses in the developing world and because of the high costs and other barriers to behavioral or biomedical interventions against HIV transmission or infection. Unfortunately, mounting difficulties seriously threaten the creation of an effective vaccine.

One significant concern is the present lack of basic knowledge needed by private enterprise to meaningfully enter AIDS vaccine development. Another concern, despite proof of principle in some nonhuman primate models, is a widespread perception that an effective vaccine against HIV is highly unlikely, will be extremely difficult to develop, and is far in the future. Surprisingly, HIV vaccine research and development programs of the NIH currently receive the least funding of any of the major AIDS research disciplines as defined by the Office of AIDS Research (OAR). Thus, the combined response from industry, Government, and the public is disproportionately low compared with the immediate and long-term public health benefits that an effective AIDS vaccine would offer worldwide.

There is a growing recognition that the NIH must now bear the major responsibility for driving research toward the development of a vaccine against HIV. The role of the NIH is particularly important since new concepts and strategies may be required to design a vaccine against this unique human pathogen. HIV-1 is a retrovirus that attacks the immune system and is distinctive in a number of ways from other viruses against which vaccines have already been developed. Making a vaccine to counter this unusual virus may require an increased understanding of the human immune system and its specific antiviral response. The role of the NIH in funding research for the acquisition of medical knowledge has become ever more critical for HIV vaccine development. Yet the NIH must be prepared to go beyond its traditional role, for the discovery and development of a vaccine demands more than just the acquisition of fundamental knowledge; it requires that the information be applied and resultant vaccine strategies appropriately evaluated. Thus, NIH-funded research must become the primary "discovery engine" to power vaccine development by the commercial sector or, if needed, by the Federal Government. Without a strong stimulus from NIH that includes much needed basic information, the waning private sector interest in an HIV vaccine may vanish altogether.

A discovery engine for an AIDS vaccine entails striking an appropriate balance between fundamental and applied research, the preclinical testing of vaccine concepts in primate models, and the conduct of human clinical trials of appropriate vaccine candidates. Having recognized the necessity for a multicomponent AIDS vaccine research and development program, the National Institute of Allergy and Infectious Diseases (NIAID) has set in place the framework for such an effort. The NIAID program represents the major scientific thrust of the vaccine effort supported by NIH. Its principal components are Basic Research, Targeted Research, and Clinical Trial networks constituting a small but well-integrated vaccine development activity. The Vaccine Research and Development Area Review Panel evaluated each of these areas separately and together.

Basic Research

The Basic Research effort, as defined by the portfolio of R01 grants encoded as AIDS/ "vaccine-related," was considered to be vastly insufficient. AIDS grants that were appropriately coded cover only a fraction of the research activities necessary for vaccine development. It became apparent during this Panel's review that some of the research that should be regarded as vaccine-related actually had been coded as Etiology and Pathogenesis and was under review of the Etiology and Pathogenesis Panel; nonetheless, many scientific aspects of vaccine research demand additional attention. Chief among these is the need for a better understanding of the immune system and its response to HIV infection, both in humans and in the nonhuman primate vaccine models. Also lacking is a basic understanding of correlates of protection and of the HIV immunogens that are required to induce vaccine responses of appropriate breadth and duration. Of particular importance are studies concerning the basic immunology of the female and male genital tracts and exploration of effective immunization routes. Attempts to stimulate interest in vaccine-related research in general (not only in AIDS) through Requests for Applications (RFAs) or Program Announcements (PAs) have been largely unsuccessful because of limited funds, the one-time nature of funding for RFAs, and the failure of many applications responsive to PAs to obtain fundable scores. In addition, the "one-time" aspect of RFAs is not, by definition, the appropriate method to maintain a sustained effort to develop a vaccine against HIV-1.

During this review it became apparent that even applications at the cutting edge of vaccine research tended to fare poorly in Initial Review Groups (IRGs) or study sections, perhaps because their empirical nature was not always appreciated by reviewers. The Panel has considered these issues at length and recommends several strategies to enhance basic research that is relevant and appropriate to HIV vaccine research and development. Although it is essential to increase the general level of support for basic research, the Panel believes that an effective solution requires more than this. The Panel is convinced that it is necessary to create a "culture" in which vaccine research is both supportable and an attractive area of research for investigators. This must be a culture that will entice leading immunologists and virologists from within and outside the AIDS field to contribute their expertise to overcome the critical and challenging problems associated with developing an HIV vaccine. Crucial to this culture is the development of a peer-review mechanism that will have the broad expertise and continuity required to evaluate vaccine-related proposals. At present, no single study section has the essential combination or depth of talents in microbiology, host defense mechanisms, immunology, and chemistry that is pertinent to vaccine biology, especially when considering an agent as complex as HIV-1. The need for vaccines in human and veterinary medicine is now so obvious that the Panel recommends the creation of a vaccine-dedicated study section. If necessary, it may be established at the expense of an existing one. Such a study section need not be restricted to research on an AIDS vaccine since multidisciplinary interactions might best be fostered by a broader approach.

Recommendations

- **Create an IRG that would be dedicated to broad aspects of vaccine research, including both HIV and other pathogens.**

- **Continue NIH/NIAID efforts to encourage and solicit the research community to submit applications in vaccine biology and immunology.**

- **Selectively target vaccine-related research areas for special consideration during review and funding.**

- **Increase the access of basic research scientists, who are interested in HIV interactions with the human immune system, to clinical materials emerging from studies within existing networks such as the Multicenter AIDS Cohort Study (MACS), the AIDS Vaccine Evaluation Group (AVEG), and the HIV Network for Efficacy Trials (HIVNET) and from certain animal model studies.**

Targeted Research

Targeted Research, as defined by the Panel, encompasses several elements within broader areas such as vaccine design and preclinical vaccine evaluation. Targeted Research can include both investigator-initiated and "directed" research activities that range from R01 grants on basic AIDS vaccine strategies to highly directed contract research mechanisms. The major programs include the National Cooperative Vaccine Development Groups (NCVDGs), the AIDS Cooperative Adjuvant Group (now largely terminated), the Collaborative Mucosal Immunology Groups (CMIGs), the Correlates of HIV Immune Protection Laboratory Contract (coded under Pathogenesis and Etiology, to be terminated June 1997), and both the Simian Vaccine Evaluation and Chimpanzee Vaccine Resource Units. Support services for these and other vaccine-related activities include a Resources Support Contract and a Preclinical Master Agreement contract program for reagents, services, and animal studies.

The Panel recognized the value of this network of resources and the continuing need for these programs. However, the links to related efforts with substantial budgets in other NIH Institutes, Centers, and Divisions (ICDs) such as the National Cancer Institute (NCI) and the National Center for Research Resources (NCRR) are not well-established, and better ways to bridge the NIAID programs to related activities in other ICDs must be found. The Panel examined the way in which animal models for HIV vaccine research have been utilized and concluded that such studies often have not been conducted in such a manner as to provide the essential information needed for vaccine development. The Panel concluded that this area requires considerably more oversight and coordination than has been applied in the past.

Recommendations

- **The Panel specifically supports and commends the recent establishment of a Vaccine Design Focus Group by NIAID. This group is composed of intramural and extramural investigators from both academia and industry who have direct**

experience in vaccine design and immunogenicity and are empowered to make appropriate priority choices.

- **The charge of this group should be expanded to an NIH-wide effort to: (1) understand the early steps in viral infection and pathogenesis in the host, (2) evaluate candidate vaccines in a systematic manner that will allow promising approaches to be identified, (3) determine correlates of immunity, and (4) establish primary (prevention of infection) and secondary (attenuation of infection such that disease is prevented and transmission is curtailed) vaccine goals. Another critical role of the expanded Vaccine Design Focus Group should be to seek out and evaluate new vaccine candidates, so that it can recommend the most promising concepts for clinical testing by the AIDS Vaccine Evaluation Group (AVEG) (see below).**

Clinical Trials

The Clinical Trials program encompasses the NIAID-supported AVEG which conducts Phase I/II clinical evaluations of AIDS vaccine candidates for safety and immunogenicity, and the HIVNET, which is designed to provide baseline seroincidence information in high-risk cohorts and support for efficacy studies. The latter effort has formal and informal links to training and infrastructure efforts of the Fogarty International Center (FIC), to cohorts for epidemiological and intervention studies supported by the National Institute on Drug Abuse (NIDA), and to studies on AIDS and sexually transmitted diseases (STDs) at the Centers for Disease Control and Prevention (CDC). Together, these sites and cohorts are well-suited to conducting the evaluation of vaccine candidates in humans.

The dilemma that now confronts both AVEG and HIVNET is related to the paucity of promising new AIDS vaccine candidates. In addition, the relative size and use of the infrastructure of HIVNET should be reexamined when vaccine candidates are not available.

Recommendations

- **AVEG should work closely with the Vaccine Design Focus Group to encourage the preclinical development of promising vaccine candidates that are suitable for clinical evaluation in Phase I and II studies as well as those that might prove worthy of evaluation for efficacy.**

  Guidelines should be established for the advancement of a vaccine product to efficacy trials sponsored by the NIH. Although the precise criteria might vary with the nature of the concept under evaluation, a product ideally should be shown to induce humoral and cellular immunity that is broad, durable, and likely to provide a significant barrier to natural HIV infection. If and when appropriate animal models become available, demonstration of protection in the preclinical evaluation with such models should support the entry of a vaccine into efficacy trials.

- **AVEG also should invest more effort on in-depth comprehensive assessments of human immune responses to HIV antigens. Greater emphasis should be placed on the laboratory analysis of immune responses in vaccinees, even if this necessitates the study of many fewer individuals with any one vaccine candidate. Among immune system parameters that should be evaluated in more detail are the generation, function, and specificity of cytotoxic T lymphocytes (CTLs); the relevance of neutralizing and nonneutralizing antibodies; the importance of Th1 and Th2 subsets of helper T cells; the targeting of immune cells to mucosal sites; the sensitivity to infection and function of antigen-presenting cells (particularly dendritic cells); and the roles of Type 1 versus Type 2 cytokines in specific and nonspecific immunity to viral infection. The participation of non-AVEG investigators in such studies is essential and should be encouraged.**

- **NIAID should rapidly reassess the status of the HIVNET program. It is likely that few expanded (Phase II or efficacy) vaccine trials will be conducted within the next 5 years; thus, a careful reevaluation of the size and nature of HIVNET programs is now needed. The seronegative cohorts that have been established for determination of seroincidence can and should be used to evaluate biomedical and/or behavioral strategies designed for reduction in HIV transmission, as has been proposed by HIVNET. If appropriately sampled, these and future cohorts also would be of value for studies of primary HIV infection and pathogenesis, and studies of early treatment of acute infection. However, because the principal mission of HIVNET has been vaccine preparedness, it is not obvious that HIVNET has the intrinsic expertise or infrastructure to move effectively beyond its original mission. This raises the question of where and how such expanded studies are best undertaken. NIAID should promptly compile a comprehensive research plan for the HIVNET effort that addresses these issues. This plan should be reviewed by a panel of experts in behavioral, epidemiologic, prevention, and pathogenesis research. The Panel also urges NIAID to prepare an overall funding strategy for HIVNET that is congruent with plans for vaccine development, and that should be reviewed by the OAR. Finally, NIAID should strengthen the ties between AVEG and HIVNET so that each group can benefit from the expertise of the other.**

In general, the Panel felt that NIAID, with additional advice and leadership, is well-positioned to assume even more responsibility for the direction of an AIDS vaccine discovery and development program. This will be aided by forming stronger partnerships with other ICDs, academia, and industry. NIAID programs currently are constrained by having insufficient funds to adequately support all areas of extramural research and development. These programs would benefit from increased flexibility in funding, the rapid deployment of resources, and the creation of new mechanisms for enhancing extramural research in areas that are vital to vaccine research and development. NIAID's efforts in vaccine research and development would be enhanced by seeking much more extensive involvement of the extramural vaccine research community in the critical decision-making process of the program.

The Panel also reviewed substantial portfolios of HIV vaccine-related activities at the NCI and NCRR and a much smaller program at the National Institute of Dental Research (NIDR). The Panel expressed serious reservations about the cost- effectiveness of these programs. The NCI HIV/AIDS vaccine effort is almost exclusively an intramural program, dependent on dispersed investigator-initiated research that is only periodically assessed by external program review. NCRR support intersects with AIDS vaccine research and development primarily in two areas: the Regional Primate Research Centers (RPRCs) and the General Clinical Research Centers (GCRCs). These Centers are training and infrastructure programs that have highly diverse AIDS components and even further variability in the amount of effort actually applied to AIDS vaccine development. The true contribution to vaccine development of the substantial NCRR expenditure coded in this area was difficult to assess, and a more thorough evaluation of the NCRR activities related to HIV vaccine research is necessary.

Recommendation

- **The Panel found NIAID's extramural vaccine efforts to be well-integrated; however, the vaccine-related activities at the NCI, NIDR, and the NCRR appear to be critically lacking in oversight and coordination. The entire HIV vaccine effort of NIH would best be coordinated by the OAR with centralization in a single ICD, such as NIAID, and with appropriate linkages to other ICDs. Establishment of such a program requires that a strong, effective, and visible leadership structure be created that includes non-Government experts who have had extensive experience in vaccine research and development. Such an organizational structure will also enable OAR to address the problems related to a balanced allocation of annual resources (and discretionary resources) where they are most needed for AIDS Vaccine Research and Development.**

Summary

The primary public health goal of eradicating AIDS nationally and globally can best be met by an effective vaccine that is safe and affordable. However, a combination of economic and scientific obstacles seriously threatens the ability to sustain an HIV vaccine research and development program. This has raised questions of whether the combined response of Government and industry has been sufficient and whether new approaches are required to promote an invigorated effort in HIV vaccine research and development. To this end, the Panel strongly urges NIH to undertake the primary responsibility for ensuring that a more vigorous and effective research program in HIV vaccines is established and pursued. This will maximize the potential to exploit the emerging knowledge needed for the future design and development of an effective vaccine. Such a program should include expanded efforts to fund basic vaccine research, a stronger and more coordinated effort in preclinical research, and an appropriately balanced clinical trial infrastructure. The OAR, in concert with the participating ICDs, must ensure that this new initiative with expanded scope is optimally structured, balanced, and coordinated. The program should be visible and guided by effective leadership that involves active participation of non-Government vaccine experts. Its primary mission should be to forge effective partnerships with the biomedical community and private enterprise that would result in development and production of an HIV vaccine for the public good.

Introduction

The Vaccine Research and Development Area Review Panel was organized on a thematic basis, covering three broad areas: Basic Research, Targeted Research, and Clinical Trials Research. Each of these areas was reviewed in depth by a subpanel which provided an evaluation and specific recommendations. From these reports, an Executive Summary was crafted reflecting the major recommendations of each subpanel along with several overarching issues that emerged from discussions among Panel members. Several problems also were identified that were not specific to vaccine research; these are grouped in the section entitled Special Issues. Some of these points resonate with the observations of other Area Review Panels (ARPs).

The major theme of this report is that HIV vaccine research and development is in crisis. This crisis currently extends from the difficulty that new vaccine concepts encounter in peer review; through the lack of coordination and a shortage of funds for targeted, developmental testing of these concepts in animal models and Phase I clinical trials; to an insufficient technical base to engage industry or private sector initiatives in meaningful vaccine development. In addition, there are administrative concerns about the distribution of funds among different competing ICDs and the relative balance between intramural and extramural funding, particularly in the NCI. The crisis in AIDS vaccine research and development requires immediate attention if we are to achieve the public health goal of halting the AIDS pandemic. Both the overall evaluation embodied in the Executive Summary and the more specific subpanel reports reflect this deep concern and have prompted recommendations that are intended to generate an invigorated and effective national effort to develop an HIV vaccine.

A. Panel Goals

The Panel was asked to review the status of current research in the field to determine what was needed for effective AIDS vaccine development, and to determine whether current funding or planned funding would meet those needs.

The Panel's initial goal was to attempt to answer a number of key questions related to HIV vaccine research in each of the following areas:

Basic Research

1. Is basic research providing the fundamental information necessary to design and evaluate AIDS vaccines? Are there gaps in scientific areas that should be addressed?

2. How can NIH encourage additional high-caliber investigator-initiated research pertinent to HIV vaccines?

Targeted Research

1. How successful are targeted research programs for HIV vaccine design? How successful are they for vaccine development?

2. Is effective use being made of animal resources for preclinical vaccine evaluation?

Clinical Trials Research

1. To what level should established infrastructures for evaluating vaccines in people be maintained considering the limited number of new vaccine candidates available for testing?

2. What other valuable research might be accomplished within these units until promising vaccine candidates are available for testing?

Additional questions spanning these areas were readily apparent:

1. What is the appropriate balance in resources allocated for investigator-initiated research, targeted research programs, and clinical trials? How should resources be allocated between intramural and extramural programs?

2. Are current funding mechanisms adequate, or are there novel funding mechanisms that would be particularly well-suited to HIV vaccine research and development?

3. How can NIH best encourage the private sector to participate more actively in HIV vaccine development?

4. Is there duplication or overlap between different programs? Is there sufficient cooperation and collaboration between ICDs and between NIH and other Federal agencies? What role should OAR play in this area?

5. What should the NIH and other agencies of the Federal Government do to collect the technical information essential to ensuring the engagement of private industry in the vaccine enterprise? What should NIH do if industry's role is even further diminished? What role(s) should NIH and the Federal Government assume in AIDS vaccine research relative to that of the private sector (industry, non-Governmental organizations, independent research institutions, international efforts, etc.)?

6. What priority should vaccine research receive relative to other AIDS research priorities?

B. Panel and Subpanel Structure and Process

Recognizing that focus on any one type of vaccine effort would be too narrow, the Panel initially resolved to establish subpanels to review three areas that roughly reflect the development of an AIDS vaccine: the basic research on AIDS vaccines, including vaccine design and discovery; targeted AIDS vaccine development focused largely on preclinical testing in animal models for safety and efficacy; and AIDS vaccine clinical trials efforts, primarily in uninfected subjects. The Panel met for the first time May 3, 1995, when tasks were assigned to individual Panel members.

A balance of expertise and research interests was considered in the selection of members for each subpanel, recognizing the potential for conflict of interest in the different scientific areas, so that competing interests might provide both a multidisciplinary and balanced review of the information. Thus, basic scientists were included in the review of the Clinical Trials Program and clinical investigators were involved in the review of Basic Research. All members had the opportunity to review all subpanel reports at various stages of development, and a consensus document was developed.

C. Methodology

The Panel reviewed extensive scientific and budgetary documents provided primarily by NIAID, NCI, NCRR, and FIC. The Panel also invited presentations from officials and staff scientists representing the above ICDs. Recent NIH program reviews by external ad hoc groups or program summaries, when available, were provided to the Panel by the ICDs as a starting framework. Additional information was provided by NICHD, NHLBI, NIDR, and NIDDK where projects were expected to have impact on AIDS vaccine research areas. All relevant recent RFAs, PAs, and contract solicitations also were provided to the Panel members by the ICDs, through the OAR. Representatives from NIAID and NCI presented update and planning information to the Panel at the July 10-11, 1995, meeting.

Budgetary information was independently confirmed by review of the ARIS database, which identified only small AIDS vaccine research efforts in ICDs other than those named above. Information about IRGs and study sections managed by the Division of Research Grants (DRG) was prepared for a subgroup of the panel.

To obtain a more complete picture of how the NIH AIDS vaccine basic science research programs relate to work supported by other Governmental and non-Government agencies, the Panel invited presentations at the July meeting from representatives from the Walter Reed Army Institute of Research, Department of Defense (WRAIR, DoD), and The Rockefeller Foundation.

Initial reports, prepared by individual Panel members, were distributed, read, and discussed at a meeting on August 30, 1995, attended by nearly all of the members. These topic reports were then fused into subpanel reports. Subpanel conference calls and electronic mail discussions of

selected topics were used to consolidate concerns. Revisions and refinements of the reports continued until all major issues were resolved.

The Panel held an open session on October 16, 1995, to hear public testimony from individuals interested in expressing their views on NIH-funded vaccines research and how it interfaces with companies and communities involved. Testimony also was solicited from a group of basic research scientists who have expressed interest, but have encountered difficulty, in acquiring funding for AIDS or AIDS-related research.

Detailed reports and specific recommendations from the subpanels are a direct result of these activities. The views of each subpanel within their specific area as well as in areas covered by other subpanels are included in this document. Thus, some overlap, as well as some minor differences of opinion, can be found in the detailed summaries. The subpanels employed different formats to best express their respective evaluations. On the whole, however, there was a remarkable degree of congruity in the overall assessment of the NIH vaccine program. This is reflected in the Executive Summary, which synthesizes the evaluations and most important recommendations of the three subpanels.

I. Basic Research Subpanel Report

Introduction

The creation of an effective AIDS vaccine requires interlocking contributions from many sectors of the biomedical research community. The role of academic scientists working in the intramural and extramural AIDS programs supported by the NIH who define themselves as "basic vaccine researchers" is to obtain the fundamental scientific information that is necessary for the rational design of AIDS vaccines. Their contributions are critical for the interpretation of information accruing from vaccine evaluation in humans and relevant animal models.

The inadequate proportion of the total AIDS research funds that have been allocated to vaccine research and development was the greatest concern identified by the Basic Science Subpanel, and this finding was strongly endorsed by the other Vaccine Subpanels. The cost of all of the NIH's AIDS vaccine programs in FY 1994 was limited to only approximately $112.9 million under the present coding system. However, this Subpanel review revealed that the true expenditure on the core topics of vaccine development was substantially less, because of the tendency to code under the category of vaccine research and development some programs that bore only a marginal relevance to the subject. It was noted that the problem of underfunding was particularly acute for unsolicited extramural "investigator-initiated" basic research projects aimed at providing the necessary intellectual framework for rational vaccine design, development, and testing. Unlike some of the programs covered by the other two Vaccine Subpanels where a more targeted or directed approach is rightly favored, basic research is most effective if it is not directed. The Basic Science Subpanel strongly endorsed the R01 mechanism for supporting investigator-initiated basic vaccine research, while recognizing that timely guidance might be provided by NIH through PAs to identify areas of research considered to be of the highest priority. Further concerns about funding basic vaccine research through existing AIDS-related study sections are discussed below.

Substantially increased support should be focused on acquiring more knowledge of the fundamental workings of the human and primate immune systems, on encouraging innovative approaches to vaccine development, and on creating novel or improved mechanisms or end points for the conduct of definitive animal trials. At this point in AIDS vaccine development, it is essential to provide incentives for the engagement of a larger group of creative immunologists with vaccine biology interests to work on AIDS vaccine issues. A "culture" needs to be created that will permit full investigation of the immunological consequences of HIV infection as well as vaccine immunization. The information gained from such studies could be vital for the continued improvement of HIV vaccine concepts.

A. Scientific Priorities: Opportunities, Needs, and Gaps

Scientific Issue from the FY 1998 NIH Plan for HIV-Related Research:

4.A More basic knowledge is needed to define protective immune responses to HIV in order to facilitate the development of vaccines and other biomedical intervention strategies to prevent and control HIV infection.

1. Host Defense Mechanisms

Status

For many years, most AIDS vaccine researchers were focused on approaches designed to induce antibodies able to neutralize cell-free HIV *in vitro*. The essential goal was that of inducing "sterilizing" immunity *in vivo*. The importance of cell-mediated immunity (CMI), particularly the role of CTLs in suppressing HIV replication, was underappreciated by many in the AIDS vaccine research community. The difficulties posed by the available assays contributed to the limited analysis of CMI responses to HIV antigens. This was a problem exacerbated by the reluctance of basic immunologists with expertise in viral immunity to join the AIDS vaccine effort. Now it is obvious that HIV has much in common with other intracellular pathogens, and thus targeting the cells in which HIV initially replicates is an important vaccine-design strategy. This does not necessarily dismiss humoral immunity as a contributor to a successful immunization stratagem; both antibody- and cell-mediated responses may be required. Recent findings indicate that the current AIDS vaccine candidates are unlikely to induce sterilizing immunity. While the induction of sterilizing immunity should remain a goal for HIV vaccine research, a vaccine that suppresses viral replication to nonpathogenic levels is arguably more achievable. This concept is already a major research focus in animal models and clinical trials. One consequence of such a strategic switch in emphasis is an absolutely compelling need to better understand T-cell responses in humans and nonhuman primates.

As most cases of HIV infection involve the sexual transmission of virus across mucosal surfaces, it is desirable for the immune system to intervene at this earliest stage of the infection cycle. This requires the induction by a vaccine of mucosal immunity, preferably involving both humoral and cellular components. Although there have been some successes in detecting mucosal antibodies to HIV after intramuscular inoculation, these responses have been generally weak and primarily limited to immunoglobin G (IgG). Furthermore, the nature and location of the cellular immune responses functioning in the genital and rectal mucosa and adjacent tissues are relatively obscure. It is essential to determine the mechanism of HIV transmission across mucosal surfaces and its initial dissemination to understand the nature of the immune responses that will be required to combat it. The contribution of the Collaborative Mucosal Immunity Group (CMIG) awards notwithstanding, the knowledge of the mucosal immune responses to different types of vaccines, and to sexually transmitted diseases in general, is limited at best. In the case of AIDS vaccines, the dearth of knowledge on mucosal immunity to HIV is particularly troubling.

Among the critical questions that remain to be answered regarding viral immunogenicity are:

- What are the true correlates of immunity against HIV infection?
- Why are neutralizing antibody titers found at only very low levels in patient sera, and why do they develop so slowly?
- Can the induction of neutralizing antibodies be improved and targeted to mucosal surfaces?
- What is required to induce CTLs and target them to mucosae?
- What is required to induce long-term memory in B, Th, and CTL compartments?
- Can improved methods be found to monitor bulk CTL activity?
- Can better reagents be generated for analyzing and manipulating the macaque immune system?
- What is the composition and role of factors (interleukins or chemokines) secreted from CD8+ cells in suppressing HIV replication? Can cells that release protective cytokines be induced by a vaccine?

Scientific Issue from the FY 1998 Plan for HIV-Related Research:

4.B The identification of viral antigens and vaccine delivery methods that elicit long-lasting protective immune responses against a broad range of HIV isolates will facilitate development of effective vaccines.

2. Vaccine Design and Animal Testing

Status

Initial AIDS vaccine candidates were based on inducing immunity to defined neutralization epitopes on the virus surface. Among these immunogens were the gp120 and gp160 envelope subunit vaccines and complex peptides designed to induce antibody responses to the V3 loop of gp120. With the appreciation that it was necessary to stimulate multiple components of the immune system to respond to multiple components of the virus, additional vaccine designs involving combination approaches were developed. These included the recombinant poxvirus-based immunogens that incorporated a subunit protein boost (the prime-boost strategy). These second-generation vaccines are worthy of continued support, but they may not induce a sufficiently powerful immune response to be the definitive AIDS vaccine. Other concepts under evaluation in animals include attenuated strains of SIV and HIV-1, following on the outstanding success of this approach in the macaque model. However, safety—but not efficacy—concerns continue to cloud the development of attenuated virus vaccines for human use. Killed virus vaccines were evaluated extensively in simian models in the early part of this decade, but protection in these models was almost exclusively associated with an immune response to "contaminating" heterologous (xeno) cell proteins in these vaccines. It is not obvious how this observation can be practically exploited for a human vaccine against natural, human-derived HIV.

A very limited number of novel vaccine designs are developed and tested each year, usually through the NIAID-supported National Cooperative Vaccine Development Group (NCVDG) cooperative agreements (U01 awards), and the Simian Vaccine Evaluation Units (SVEUs), in the NCRR-supported RPRCs or in the intramural research programs of NCI and NIAID. Often

these approaches have little or no private sector support to enable the development of clinical-grade vaccine products for human testing. Because the science and knowledge base at present is insufficient to engage meaningful participation of the private sector in HIV/AIDS vaccine development, it is essential that NIH assert leadership for the collection of information essential to bridge the gap between basic research and industrial product development, an area that is definable as targeted research. If the private sector fails to respond to evolving opportunities in vaccine discovery and development, the NIH should take responsibility for development of immunogen design and product production. Facilities administered by the NIH or the DoD could be used to prepare clinical-grade candidate vaccines, at least for pilot lots. Alternatively, vaccine production could be allocated to the private sector under Government contracts.

Basic research on vaccine adjuvants has been focused primarily on the empirical testing of products, rather than on defining and understanding their mechanisms of action. How most vaccines containing adjuvants engage and stimulate the immune system to produce greater and more appropriate immune responses than aqueous preparations is an important area in which knowledge and understanding is lacking. Neither is it clear what effect adjuvants have on the conformation of complex glycosylated proteins such as HIV-1 gp120 or gp160, either as subunit proteins or as part of virion or pseudovirion structures.

In the absence of any "perfect" animal model for human AIDS, it was initially appropriate to evaluate rigorously the characteristics of as many plausible models as possible. The inevitable consequence of this policy is that, in the simian model alone, there are now too many different test monkey species and too many different SIV and HIV-2 challenge stocks for all the models to be sustained at adequate levels of funding. Distributing what are inevitably limited funds among too many models has not permitted any of them to be characterized in as much detail as desirable. Furthermore, vaccine experiments in primates tend to use only a few monkeys per experiment, which usually leads to nondefinitive end-points and a limited opportunity for followup analyses. While this is understandable for experiments on chimpanzees because of their restricted availability and cost, it would certainly be feasible to conduct critical basic research experiments on a larger scale with macaques if funds were available. (See further discussion in the section on targeted vaccine development.)

The issue of HIV variation has always been a critical one in the development of an effective AIDS vaccine. HIV varies within an individual, within populations in a geographically restricted area such as the United States, and among different areas of the world. Hence there is substantial concern over the impact of HIV variation on the development of an effective AIDS vaccine. Nine major envelope sequence subtypes or clades within what is now known as the Main (M) group of HIV-1, designated A through I, have been identified, along with a separate, highly divergent group of strains referred to as the Outlier (O) group. Almost all documented HIV-1 infections within the United States have been B-subtype strains, but rare cases of infections with strains from the A-, D- and E-subtypes have been identified in North America. Early predictions that variation in the HIV-1 *env* gene would continue to increase at about 1 percent per year have been borne out, and there is every reason to expect that the recognized subtypes will continue to be disseminated, both globally and within the United States. While a limited degree of cross-subtype virus neutralization by some HIV-1+ sera has been observed, its significance for vaccine development is not yet clear. There is an imprecise concordance

between neutralization serotypes and the genetic subtypes, and much remains to be learned about neutralization and whether a vaccine can be developed to induce such cross-neutralizing antibodies.

An extensive and expensive framework for performing vaccine studies in animals and humans has been put in place without adequate funds or mechanisms to generate vaccine concepts and products necessary to utilize this framework efficiently. In contrast, it was estimated by the Panel that the annual cost of the unsolicited R01s ($8.6 million) and other grants ($1.6 million) in the portfolio on basic and preclinical vaccine research, including some animal models research, was about $11 million in FY 1994. This was less than 10 percent of the total AIDS vaccine research and development budget for that year. This is in stark contrast to the greater funds allocated to contract-supported preclinical testing in animal models, clinical trials, and vaccine trial training and infrastructure. (See accompanying reports from the other Vaccine ARP subpanels.) The extensive commitment of vaccine-related funds to mechanisms other than R01s is evident, and the Panel felt strongly that this imbalance should be redressed. It was recognized that other solicited, investigator-initiated programs also support basic as well as preclinical vaccine research: the NCVDGs, funded through the U01 mechanism, and the CMIGs, interactive R01s funded through an RFA, as well as some intramural projects. Further, the Panel noted that several areas of basic research related to vaccine development that is likely to be funded by R01s, such as the mechanisms of antigen presentation, mucosal immunity, and human immunology in general, have probably not been coded by the ICDs as vaccine-related, and perhaps not even as AIDS-research related. Problems in coding research accurately were a recurrent theme that hindered the Panel's ability to gain a precise picture of the scale of basic research relevant to AIDS vaccine development. Nevertheless, the shortage of unsolicited investigator-initiated research in HIV vaccine research is critically low and this category of research has been identified as a high priority for increased support.

B. Review of Vaccine Research and Development at the NIH by Scientific Priorities

1. Host Immune Defense Mechanisms

Considering those grants identified by the Division of AIDS (DAIDS), NIAID, to be part of the AIDS vaccine research and development portfolio, the Panel felt that there was an overemphasis on humoral immunity at the expense of studies on cellular immunity. At least seven independent groups are currently funded to develop and characterize human or rodent monoclonal antibodies to HIV proteins, while there is significantly less emphasis on approaches to induce and characterize effective cellular immune responses to HIV or its antigens.

The contribution of the CMIG R01 awards to the overall portfolio ensures that mucosal immunity is evaluated to some extent. However, it is not clear how these grants will fare in recompetition. It was not determined whether NIAID or other ICDs plan to continue specific set-aside funding to this area. Because the induction of mucosal immunity by an HIV-1 vaccine may be essential to its success in preventing or limiting sexual transmission of HIV, research in this area must remain a high scientific priority.

2. Vaccine Design and Animal Testing

A reasonable number of grantees are slowly developing new immunogens for vaccine development. However, there still appears to be too much emphasis on subunit vaccines or chimeric proteins and too little on more imaginative approaches. Nonreplicating vaccines based on the expression of a small fragment of the HIV-1 core or envelope proteins, especially from the variable regions of gp120, are unlikely to induce an immune response of sufficient breadth or potency to mediate significant protection from HIV. Almost all of the "live" vector approaches currently being pursued involve poxvirus variants; other vectors should be pursued and supported.

Research on adjuvants was relatively well-supported by NIAID in 1994, mostly under U01 Cooperative Agreements or a Simian Vaccine Evaluation Unit contract rather than through the R01 mechanism. However, these grants have expired and most have not competed successfully in the IRGs. This may create a shortfall of research in this important area.

Recent studies supported by NIAID and other organizations such as the World Health Organization (WHO) have indicated that the envelope subtypes defined by genetic sequencing do not correlate with neutralization serotype, despite both qualities being based on properties of the viral envelope. Although neutralization serotypes clearly exist, their number and compositions remain uncertain; there is an imprecise concordance between neutralization serotypes and genetic subtypes. This is not to say, however, that the genetic subtypes have no relevance to vaccine development: First, they can influence neutralization serotypes, and second, the CTL response is directed at linear epitopes. Variation in the presentation of these subtype epitopes to the individual's immune system is likely to correspond very closely to the subtype-defining, primary genetic sequence variation.

Notwithstanding the major problems imposed by HIV-1 sequence variation, the Panel considered that this issue could almost be considered secondary to that of creating a vaccine able to prevent or limit infection even of an HIV-1 strain of a genotype closely related to the immunogen. However, the subtypes of HIV-1 strains, defined by genetic sequence, that are circulating at the likely site(s) of vaccine efficacy trials should be taken into account at the time the immunogen is prepared. There is a compelling case that efficacy trials are best conducted in areas with the highest rates of incident infections. This is not likely to be within the United States or other countries within the highly industrialized world, where HIV-1 strains with envelope sequence subtype B predominate. Thus, future immunogens might be based most usefully on the (almost exclusively non-B) envelope sequence subtypes that are endemic to potential international test sites. That the subtype of a test immunogen is not necessarily matched to virus strains circulating in the United States should not preclude its initial evaluation for safety and immunogenicity in Phase I trials in this country. Information gleaned from these initial trials could readily be used to determine whether further trials of the concept would be warranted in the geographic area for which the immunogen was initially designed. Finally, a multivalent vaccine is likely to be needed for citizens of any country engaged in global travel or business in the international community.

The Panel felt that a better return could have been received from the enormous investment that has been made by NIAID, NCI, and NCRR in nonhuman primate models for HIV vaccines. A serious problem imposed by the present structure of funding nonhuman primate model research is that the traditional level of funding available through the R01 and U01 mechanisms is too low to permit examination of more than approximately two or three variables, and appropriate controls, during the 2- to 3-year life span of projects. NCVDG funding is presently at a level that permits, on average, the use of 12 monkeys per year. The effect of these restrictions is that experiments often contain a number of experimental and control animals inadequate to obtain definitive end points. Historically, this situation has caused significant problems of data interpretation, and the Panel felt that it would be wrong to repeat the errors of the past. It has been argued by NIH program administrators, and supported by study sections, that general increases in the funds available for nonhuman primate studies through the R01 or NCVDG mechanisms would be wasteful in the long run, given that most of the experimental approaches will be failures. However, a definitive end point can often be valuable, even if the approach under evaluation is an intrinsic failure. Too often, nondefinitive end points are reached with small animal studies that are ultimately a wasted effort or that turn out to mislead the field, causing even greater losses.

In an attempt to confirm or refute initial findings in animal models that are made by NCVDGs and other investigator-initiated programs, the Master Contract mechanism was developed. In the past, this system has involved DAIDS Program Staff deciding internally whether or not to provide additional support for concepts they deem to be sufficiently promising. The Panel has learned that funding has been provided for 410 monkeys via Master Contracts, a significant multiple of the number of animals supported by investigator-initiated funding mechanisms. The Panel viewed the Master Contract procedure as laudable in principle but having potential shortcomings in practice. The Panel believes that external review of administrative decisions is essential, given the scale of the awards being made. The recently established NIAID Vaccine Design Group may resolve concerns about this issue.

C. Review of Vaccine Research and Development at the NIH by Institute, Center, or Division (ICD)

1. NCI

In FY 1994, NCI spent in excess of $16 million on projects that were defined as relevant to AIDS vaccine research and development. These projects are conducted both on the central NIH campus in Bethesda and at the Frederick Cancer Research and Development Facility (FCRDC). Basic, preclinical, clinical, and animal model research activities contribute to the overall program. Experimental approaches include vaccination with cellular antigens, peptides, DNA, pseudovirions, recombinant adenoviruses, or poxviruses.

Until 1990, the vaccine-related programs at NCI were organized as an AIDS Task Force. This was disbanded and currently there is no central organization of the programs and no attempt to coordinate them towards a common goal. Indeed, even within the geographically restricted

FCRDC site, cooperation between the various groups appears to be minimal or nonexistent. There have been only limited attempts to coordinate studies between NCI and NIAID or NCRR. The justification provided by NCI for its current structure is that the individual groups are considered to be conducting investigator-initiated research programs that neither need nor would benefit from any central direction. This was seriously questioned by the Panel.

The Panel had many concerns about the way in which the NCI AIDS vaccine research programs were organized and conducted. In principle, investigator-initiated research intramural programs can play a key role in the development of an AIDS vaccine. However, the analogy drawn by NCI between the NCI intramural programs and extramural investigator-initiated programs was considered by the Panel to be inexact and inappropriate. Extramural programs are subject to prospective, expert peer review from other AIDS investigators. The Panel was concerned that, while the NCI vaccine programs were peer-reviewed, they have not been reviewed as vaccine programs per se. This was an inevitable consequence of the lack of central organization of the NCI AIDS vaccine research programs; the individual programs often were reviewed as minor components of a larger entity, with a consequent lack of specialist input. One consequence of this system is that NCI has no means to assess the relative merits of the individual vaccine research programs it administers. This lacuna would clearly hinder any internal attempts to prioritize those programs to preserve under conditions of greater financial stringency than apply today.

The Panel recommends an expert peer review of the entire vaccine research program administered by NCI as soon as possible. In the absence of such a comparative review, the Panel was able to provide only general opinions on the value of the individual vaccine research programs within this Institute. Within these limitations, the overall quality of the NCI vaccine research programs was considered mixed. There are clearly projects that are highly rated and internationally competitive, and there are others that are not contributing significantly to either AIDS vaccine research or even to AIDS-related research. Although many of the programs raised concerns, better quality programs included those on virion-associated cellular antigens and their roles in protection against SIV, the DNA vaccine program, collaboration on the *Macaca nemestrina* model with NIAID-sponsored groups, collaborative studies on poxvirus vectors that help underpin the prime-boost vaccine strategy, and a peptide vaccine program.

The Panel reviewed the titles and abstracts of those intramural projects deemed by NCI to be AIDS vaccine-related at both the Bethesda and Frederick campuses. It was clear to the Panel that many of the projects are, at best, of only indirect relevance to AIDS vaccine research and development. At least two projects at Bethesda focused on vaccines against cancer; other projects are designed to characterize the basic molecular virology of HTLV-1 and to develop an HTLV-1 vaccine. There also are projects to study the functions of HIV-1 regulatory genes and sequences and to develop antisense oligonucleotide and gene therapy antiviral strategies. While plausibly promising projects, these studies are considered to fall outside the definition of AIDS vaccine research and should not be considered as part of the NIH AIDS vaccine research budget. Indeed, some of the studies should not be considered part of the AIDS research budget at all. A preliminary estimate is that up to half of the total budget that was classified by NCI as AIDS vaccine research and development (in particular, $6.3 million indicated only as Operations and Technical Support) may have been misclassified. The Panel also expressed

concerns about the scale and nature of several of the support contracts awarded to Bethesda-based biotechnology companies ($1.9 million) and considered that the value and need for these contracts should be closely scrutinized before they are recompeted.

It is clear that the FCRDC has virus, antigen, and antibody production facilities that are unique among NIH-supported programs. These facilities could be a critical national resource for any centrally directed national program to develop an AIDS vaccine. Some NCI-supported scientists, especially several of those groups working at the FCRDC, could make vital contributions towards such a program. However, the Panel felt that, at present, the NIH was not receiving sufficient return on an annual investment of over $14.8 million in the NCI AIDS vaccine programs to warrant continued support at this level. The Panel recommends cessation of the use of AIDS monies for projects not pertinent to AIDS vaccine development and critical review of the remaining projects within the NCI to allocate resources where they might be most productive for the HIV/AIDS vaccine efforts.

2. NIAID

The NIAID intramural program on HIV vaccine research development is smaller than the NCI program: Yet, the intramural AIDS vaccine research projects (Z01 awards) at NIAID received $7.2 million in FY 94. The Panel did not examine these programs in any rigorous sense, because a detailed project review was beyond the scope of this review. However, it noted that the intramural budget for HIV/AIDS vaccines was nearly equivalent to the entire portfolio of extramural R01 grants in basic and preclinical vaccine research ($8.6 million). The Panel recommends that a future review of intramural research at the NIAID be conducted under guidelines similar to those recommended above for the NCI intramural programs. Again, the Panel noted that several of the NIAID intramural programs classified as AIDS vaccines research, including some intramural contracts, bore only a tenuous connection to the subject, at least in so far as could be judged from the titles and abstracts of the awards. For example, research on the mechanisms of pathogenesis of murine leukemia virus-induced "AIDS" in mice might be more appropriately coded under AIDS etiology and pathogenesis. Similarly, a major program on the molecular genetics of eukaryotic cells and their viruses has yielded outstanding results but is mostly directed at topics more closely related to HIV pathogenesis. The Panel was concerned that such misclassification within the intramural programs leads to the perception that more AIDS resources are allocated to vaccine development than is truly the case.

In FY 1994, a total of $4.34 million was allocated to Research Management Support for AIDS vaccine research, the administrative costs of the many vaccine programs supported by NIAID. In addition to support for grants and contract management, this budget covers workshops, meetings such as the NCVDG, and travel for extramural investigators advising NIAID and is proportional to its role in extramural funding.

3. NCRR

The Regional Primate Research Centers (RPRCs) funded by NCRR constitute a critical national resource for AIDS vaccine development. When the AIDS problem was recognized, limited expertise in viral diseases was in place at many of these facilities to take immediate advantage

of these resources. As the priorities for use of these Centers began to shift to AIDS research, supplemental funds were initially added to support these new priorities. Some additional funds were subsequently included in the Base Grants to the RPRC, but these supplemental funds did not keep pace with the growth in the rest of the AIDS research field. Individual centers focused on gathering basic data in many different SIV models, which led to a proliferation of SIV, mutant SIV, HIV-2, and SHIV model systems. This has been extremely valuable for studies of viral pathogenesis as well as vaccine research. The differential pathogenicity observed in these models now needs to be exploited with in-depth immunological studies and comparative studies of vaccines tested under different "stringency" of pathogenic challenge now possible with the range of viral strains available.

There is a need for the RPRCs to be more proactive in (1) the development of refined and comprehensive studies, particularly involving immunologic analysis, (2) incorporation of outside complementary expertise to enhance the scientific breadth of studies, and (3) an effective policy that makes these animal resources and facilities, as well as viral resources, even more accessible through competitive peer-reviewed research from the broader scientific community. The Panel noted that the directed programs of the Medical Research Council of the United Kingdom in association with the primate centers of the European Economic Community (EEC) have yielded a high return from a relatively small investment of targeted funds. The European consortium has developed a supplemental reimbursement system for funding cross-center collaborative vaccine studies, which are conducted in addition to center-specific studies.

D. Special Issues

1. Administrative Aspects

The Panel was, in general, satisfied with the way in which the limited resources designated as basic AIDS vaccine research were distributed by NIAID, and by the proactive approach of the Program Staff of the Preclinical Branch of the DAIDS, NIAID, in supporting investigators with novel ideas and approaches. However, it was demonstrated to the Panel that investigator-initiated R01 applications that propose testing or comparative studies of the immunogenicity of different immunogens or adjuvants in whole animals (even mice) tend to compete poorly in Initial Review Groups or study sections, compared with projects with a more molecular or mechanistic focus in immunology (e.g., transduction factors, signal transduction, activation of membrane receptors, etc.). Even more worrisome is that projects to define basic principles of immunogenicity and tolerance induction in humans and nonhuman primates are often viewed by IRGs as "lateral" research, i.e., merely extending or translating principles established in mice to other species. This has occurred despite repeated indications that human and murine systems are divergent in many aspects that dramatically affect lymphocyte development or induction and maintenance of immunity to specific antigens or pathogens. As a result, basic immunogenicity issues that are fundamental to vaccine development, not only for HIV but also for other pathogens, remain poorly supported and fail to attract many of the best established

immunology and virology laboratories as well as many of the best young investigators in these fields.

Assessment of the current portfolio of grants administered by the Vaccine and Prevention Research Program of the DAIDS is complicated by the grant-coding system currently in use. Under the current system, many awards to study human immunology (particularly CTL research) and the mechanisms of HIV transmission and pathogenesis are designated to categories other than those dedicated to vaccine research. It is probable that many of these grants have been classified as "etiology and pathogenesis" or, in the case of awards for understanding human immunology, classified as non-AIDS and not reviewed by any of the Area Review Panels. While the Panel was not overly concerned about these administrative minutiae, they did affect its ability to gain a good understanding of the scope of current basic and preclinical, vaccine-related research.

Increasing the pool of resources available for investigator-initiated basic and preclinical vaccine research through the R01 mechanism—the principal need identified by the Panel—will be difficult without a substantial infusion of additional funds, either *de novo* or from other research activities. The Panel considered that the true scale of the deficiency in grant funding is even worse than it might seem, because of techniques used to artificially inflate the number of grants funded and give the false impression that more work is being conducted than is actually the case. For example, although an extremely low proportion of highly rated R01 applications is presently funded, this proportion is also inflated by the present policy of cutting funding for successful applicants by 17 percent or more and by delaying their start dates to release funds for additional awards.

The Panel also felt that the interactive research project grants (IRPGs) using the R01 mechanism to conduct collaborative multidisciplinary studies of potential AIDS vaccines is not working well and that this should be rectified by increased use of U01 or U19 cooperative agreement awards or by reconfiguring the IRPG/R01 mechanism and its review. The principal value of the IRPGs is to realize the political aim of funding a greater number of R01 grants. But, review committees do not always evaluate or appreciate the requirements for the collaborating entity before deciding the merit of the individual awards. For example, it is much harder to obtain adequate funding through the R01 mechanism of the IRPG for the vital but scientifically less intriguing grants that largely provide critical cohort maintenance and sample acquisition.

The Panel received information from DAIDS as to how the issue of R01 underfunding was being addressed. This included the use of Select Pay with oversight by the NIAID Advisory Council, which the Panel endorsed under certain circumstances. However, the Panel urged a widespread dissemination of the criteria used by staff to determine the suitability of an award for Select Pay, because these procedures are poorly understood.

The RFA mechanism for targeting vaccine research was supported in principle by the Panel, provided that the standards of solicited awards remained reasonably high and comparable to successful unsolicited awards. For example, the Panel considered it advisable to retain the current policy whereby a fixed sum is not preallocated to an RFA; only those proposals

considered sufficiently meritorious should be funded. The former policy of large set-aside funds allowed many less-deserving awards to be supported.

The Master Contract mechanism provides a third means by which DAIDS staff have responded to the shortfall for specific needs not met by R01 funding; the operation of this mechanism is also discussed below and in the section on the Animal Models Programs. The Panel considered NIAID's establishment of the Vaccine Design Group as a positive step towards the external oversight of development and analysis of new immunogens. However, without adequate financial resources at its disposal, the potential of this group may not be fully realized.

E. Conclusions and Recommendations

Recommendations by Scientific Areas

- **NIH should increase total funds allocated to basic research in support of vaccine design and development. In particular, basic research on immune responses in humans and macaques should be targeted as an area of the highest priority.**

- **The Division of Research Grants (DRG) should develop a newly configured separate study section for vaccine-related research.**

  The obvious solution to address a deficiency in a specific area of research is a separate study section for that area. Separate, ad hoc study sections, such as those that have been constituted for review of RFAs, do not have continuity built into their structure and thus fail to address the long-term practical issues associated with flexibility for consideration of newly emerging concepts and reevaluation of revised applications. A continuing study section on vaccines would require a very broad expertise in many related areas.

- **NIH should allocate specific funding for vaccine-related research to stimulate the fundamental research needed in immunology and vaccine design.**

  Even if a new permanent Vaccine Study Section could be established in the near future, the problem requires an immediate intervention. The ICDs, in collaboration with OAR, should be encouraged to allocate a defined amount of funding in each fiscal year for targeted areas of basic research that are specified as high priority for vaccine development. All grant applications that are received would be examined for their relevance to these areas and would be designated for special consideration by DRG staff and the chair of the study section. The study section members reviewing the application might be requested to give the grants a "relevance score" from 1 to 5 based on their perception of the application's relevance to the targeted areas. The study section would be informed that these designated applications would be funded from the separate allocation of funds, because this research was a national priority. The payline for these applications might be much higher than the payline for all other applications reviewed by that study section. Care should be taken by DRG, ICD, and OAR staff to recognize artificial maneuvers to

utilize "buzz words" in the abstracts or Specific Aims that trigger designation for targeted review. Placing applications in this separate category should be done thoughtfully and fairly, and should also involve input from the chair of the study section at the time of the review.

The Immunobiology Study Section or the AIDS-related Research-A (ARRA) study section might be an appropriate study section for these grants; if necessary, a few new members could be added with specific expertise and interest in vaccines.

- **All future research devoted to the development and analysis of vaccination strategies should involve forging more extensive collaborative links with cellular immunologists.**

  This applies to both nonhuman primate and clinical human AIDS vaccine trials, and could enable a better understanding of the consequences of immunization. It is recognized that many of the leading immunologists in the United States have not been involved in AIDS vaccine research to any significant extent. The Panel felt that it is vital to develop ways to change this situation. A culture must be created that will lead to improving our understanding of immunogenicity to viral antigens. Thus the Panel strongly recommends development of funding mechanisms designed to attract creative young investigators and experienced immunologists to this complex and challenging area of research.

- **Clinical samples, from vaccine trials and relevant NIH-supported natural history cohorts, as well as viral stocks for experimental animal models, should be made more readily available to researchers, with appropriate research plans, outside the groups involved with the initial sample and data acquisition.**

  Approval of these plans should fall within the purview of an independent committee, and not, as at present, solely under the control of the group which has collected the samples. The supply of materials available, and competing demands upon them, should be taken into account. The Panel noted the success of the NIAID AIDS Reference and Reagent Program in providing virus stocks and other reagents obtained from clinical sites and basic researchers for distribution to the research community.

- **NIH should reevaluate the relative distribution of resources between clinical evaluation of current vaccine candidates and the development of new ones with potentially greater promise. Redundant funding for clinical trials of similar vaccine candidates should be eliminated in favor of new vaccine concepts. NIH should establish mechanisms for identifying novel approaches to vaccine development and rapidly testing their feasibility.**

- **NIAID and NCI research programs on HIV-1 genetic variation should be better coordinated, both within the NIH and with other agencies pursuing this problem, including the DoD, CDC, EEC, and WHO.**

  Although NIAID has been proactive in this regard, HIV genetic variation research programs of the newly created HIVNET are likely to duplicate other activities already

supported by NIAID, including NIAID-sponsored work by the WHO (WHO AIDS research activities will be subsumed within a new United Nations structure, the UNAIDS Program, during 1996).

- **A rationalization of the simian animal model field and a redistribution of funding for a significant fraction of the current animal models is imperative. The Subpanel recommends performance of fewer, but more detailed, studies, each using an increased number of animals.**

  A top-level, independent expert group (see the Targeted Vaccine Subpanel Report) should develop criteria for the continuation or expanded utilization of an animal model in vaccine research and determine which of the current models meet those criteria. Among the current simian models, there is a spectrum of viral virulence and consequent pathogenicity. Some virus strains in some animals replicate only to low levels, cause only limited disease, and tend to be relatively easy to protect against infection by immunization with SIV antigens. Conversely, other models replicate to high levels *in vivo*, cause rapid disease, and are hard to protect against. The Panel felt that, in principle, it was important to retain one simian model at each end of the spectrum and perhaps one in the middle for larger comparative vaccine studies. When developing a new vaccine concept, it is advantageous to show that it confers protection under favorable conditions, yet a rigorous test of the concept is also important. The considered development and use of assays to measure virus load in plasma and tissues is essential for assessing the comparative worth of simian models and for determining the outcome of vaccine trials.

- **NIH-supported basic vaccine research on the HIV-1/Chimpanzee model should focus almost exclusively on the development of a challenge strain that would replicate to high titers in these animals and cause disease.**

  The current stocks of virus that replicate poorly in chimpanzees have limited value, except for initial "proof of concept" studies.

- **NIH should continue to encourage the use of small animal models (such as cats and mice) for the development and assessment of vaccine concepts.**

  These animals provide the opportunity to examine large numbers of variables and group sizes in a relatively short time frame and at relatively modest cost. However, the value of large-animal studies not involving primates or an SIV or HIV challenge should be judged critically for their potential contribution against the substantial cost of these models.

Recommendations on Administrative Issues

General

- **NCI and NIAID should reevaluate their code assignment procedures to ensure that a more accurate representation of what basic and preclinical research is devoted to the NIH vaccine program.**

  The Panel believes that the approximately $113 million sum defined as the cost of the vaccine research and development by NIH for FY 1994 significantly overestimated the true expenditure on these programs. Miscoding also might have underestimated the expenditure on basic research in some areas of immunology.

- **NIH should place a very high priority on the creation of a new study section dedicated to fundamental vaccine research topics, either *de novo* or from existing AIDS-related study sections.**

  OAR should work with DRG to ensure that this is done as rapidly and as efficiently as possible. The academic standards of successfully competing awards should be maintained in vaccine research at a common, high level, as in all areas of AIDS research. Because some vaccine research may not be considered cutting edge science by the existing study sections, the new study section should include individuals who recognize the imperative need for translational research in vaccines. Such individuals should be sought to ensure adequate unsolicited R01 funding.

- **Both NIAID and NCI should minimize the amount of funds allocated by Program Staff without outside peer review from contractual or other resources available within these Institutes.**

  A detailed breakdown of such supplementary funds should be provided to OAR on an annual basis. Distribution of funds through the Master Contract (in NIAID) and other contracts in NCI should be determined by a review group comprised of both intramural and extramural scientists, in addition to NIH Program Staff and administrators.

NIAID

- **A relatively small sum of seed money (perhaps derived from the OAR Director's Discretionary Funds) could be placed under the control of an expert peer-review group, specifically to allow vaccine concepts to be evaluated in primates before submission of a more formal research proposal.**

  The Panel fully appreciated that the R01 mechanism was not necessarily the most suitable way to fund some key areas of AIDS vaccine research and development. Vaccine research can have an empirical nature that is not well-recognized by study sections, and can be unusually expensive compared with certain other areas of AIDS research. A less abstract problem is that study sections require, not unreasonably, evidence of preliminary data that

support the feasibility of a concept under review. Without such data, an application may well be denied funding, irrespective of its intrinsic merit. Yet without such funds, it may be impossible to obtain appropriately convincing data, especially if experiments involving primates are necessary. This vicious cycle needs resolution.

- **Basic research activities should not be supported under the existing contract mechanisms.**

  Contracts are time-consuming and expensive to compete for and to administer, both in terms of financial costs and of demands on scientists' time. The necessarily rigid legal constraints imposed by the nature of a contract are not always compatible with the flexibility that is an integral component of cutting-edge research. NIAID basic vaccine research funds currently allocated to contracts should be shifted to grant mechanisms. Targeted R01 awards or cooperative agreements (U01s) were perceived to be superior mechanisms for enabling key areas to be studies, while allowing investigators the independence to achieve scientific goals in the way they consider most appropriate.

- **The Panel urges Review Committees and Program Staff to recognize the clear requirement for more support for investigator-initiated research in both basic and applied studies in human and nonhuman primates and encourage approval of the necessary support in appropriate circumstances.**

  In many cases, small-to-medium-sized R01 grants are suitable, and the scientific return on such investments can be considerable. However, funding limits often preclude the support of such studies through the conventional R01 mechanism. Three mechanisms by which adequate resources might be obtained are: increasing the funding ceiling on R01 awards under certain circumstances; reinstituting Program Project (P01) awards similar to those provided by other ICDs; and increasing funds for NCVDGs or unsolicited cooperative agreements (U01s).

- **The U01 and U19 mechanism used to support the NCVDGs for conducting multidisciplinary studies of potential AIDS vaccines merits increased support, whereas the interactive R01 mechanism for multidisciplinary studies should be abolished.**

  The U01 and U19 cooperative agreements retain administrative flexibility and encourage cross-talk between basic research investigators and preclinical study investigators. However, the Subpanel was particularly concerned that the current cap on funds for these awards precludes or substantially limits basic concept testing in primate models.

- **To enhance the functioning of both the vaccine development oversight group proposed above (discussed further in the Targeted Vaccine Research Subpanel report) and the efforts of extramural investigators, NIAID should establish and monitor a comprehensive computer database for recording and analyzing information derived from vaccine trials in animals and humans.**

This information should be routinely available to all grantees involved in AIDS vaccine research to permit coordinated efforts to critically evaluate different experimental approaches and develop valid cross-comparisons of data.

- **The need for an RFA should be reviewed by an expert group comprised of both extramural non-Government scientists and DAIDS Program Staff.**

  The charge to that group would include a careful review of study section-approved proposals to address whether work supported by the proposed solicitation would overlap with other supported or planned programs. NIAID should retain its current policy of funding only those proposals considered sufficiently meritorious and not pre-allocating a fixed sum to an RFA.

NCI

- **NCI should immediately conduct a rigorous review of all components of its intramural program presently designated as contributing to AIDS vaccine research and development and use this review to determine which of its current vaccine-related programs should be preserved, and at what level of support.**

  The Panel was concerned that many projects coded in this area bore little or no relevance to the reality of vaccine research and development. Thus their inclusion within the vaccine budget substantially distorts the perception of the actual NIH effort expended on vaccine development. Indeed, a substantial proportion of dollars assigned to NCI intramural vaccine research probably should not be considered as AIDS-related in any sense.

- **The Subpanel proposed that AIDS vaccine research activities of the NIH might best be served if the most relevant and competitive intramural programs at the NCI were placed within a single Division, with administrative control by the OAR, with the view of assimilation into the NIAID intramural program.**

  In nearly all cases, it should be possible to achieve this goal without the necessity for physical relocation of any research groups. The facilities at the FCRDC could be used for a targeted, coordinated national effort towards developing an AIDS vaccine. At the very least, the coordination of AIDS programs at NCI needs to be under the administrative review of the OAR until the creation of a unified, cohesive AIDS vaccine program within the NIH.

II. Targeted Research Subpanel Report

A. Scientific Priorities: Opportunities, Needs, and Gaps

Scientific Issues from the FY 1998 NIH Plan for HIV-Related Research:

4.A More basic knowledge is needed to define protective immune responses to HIV in order to facilitate the development of vaccines and other biomedical intervention strategies to prevent and control HIV infection.

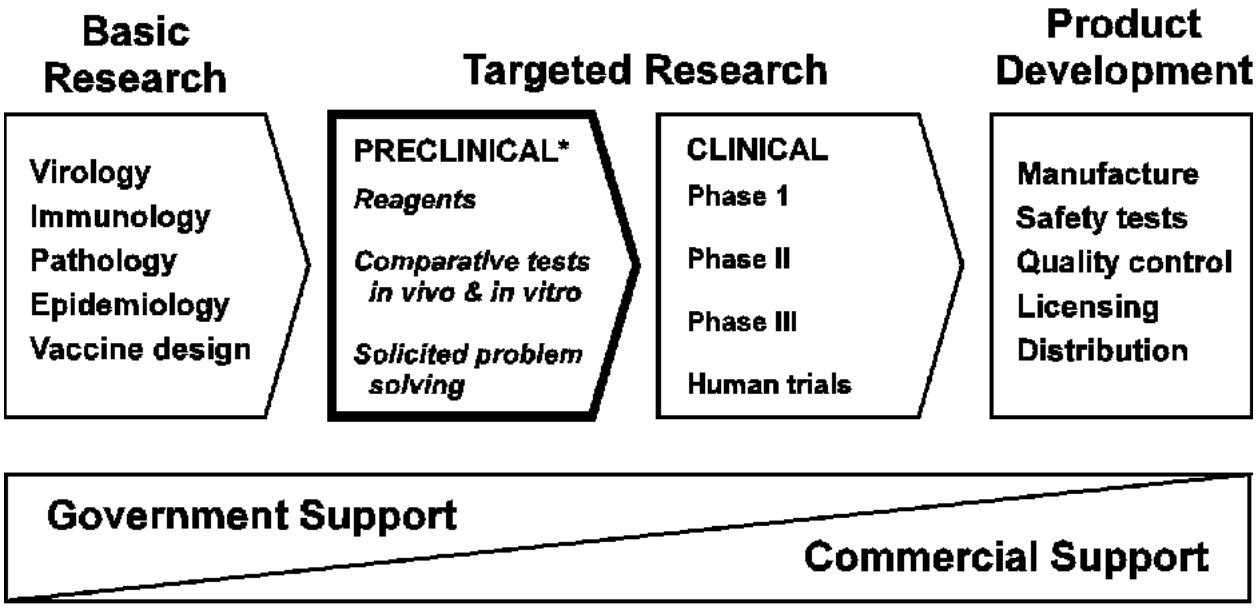
4.B The identification of viral antigens and vaccine delivery methods that elicit long-lasting protective immune responses against a broad range of HIV isolates will facilitate development of effective vaccines.

1. Status

Targeted Research: The Link Between Basic Research and Industrial Product Development

Targeted research involves the design of vaccines, preparation of suitably characterized viral challenge stocks, and preclinical evaluation of vaccines in animal models (See Figure 1, second box from left). In reviewing the status of NIH-sponsored vaccine research, the Panel found a critical need for a strengthened program on targeted vaccine development. The Panel therefore recommended the creation of a strong, targeted vaccine initiative to provide an essential, currently missing bridge between NIH-sponsored basic research and commercial product development.

Figure 1. Targeted Research
A Key Link Between Basic Research and Industrial Product Development.



***This section of the report addresses Preclinical Targeted Research**

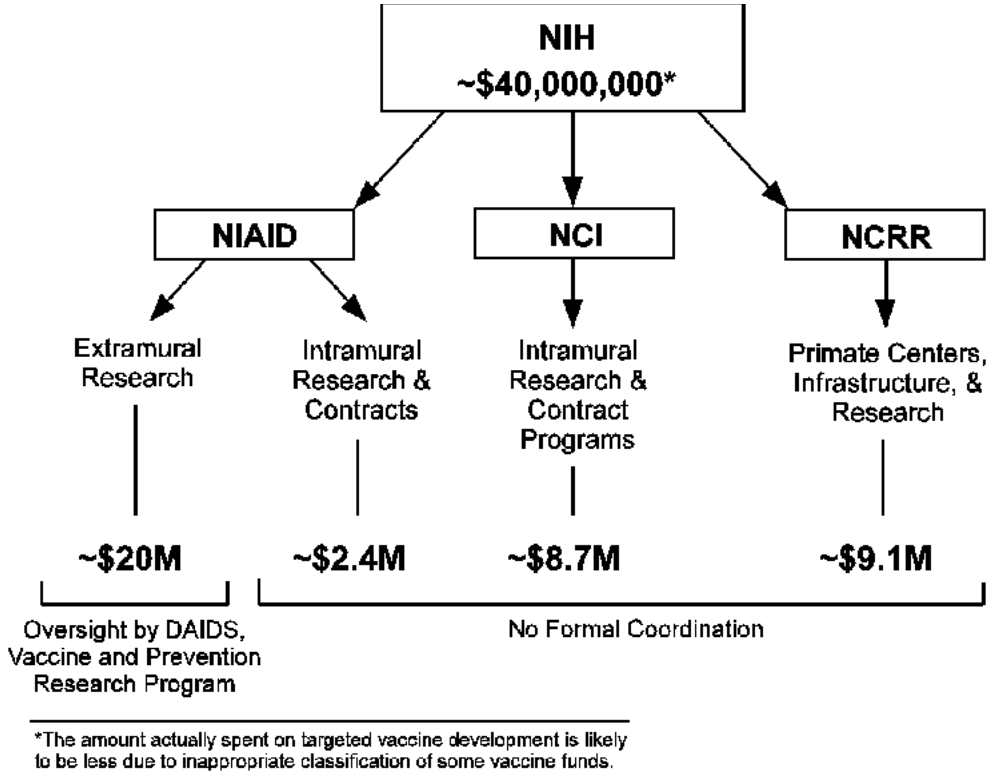
Early stage vaccine development and basic vaccine research, which has historically been the strength of the NIH, is distinct from commercial product development. The latter relies on and is made possible by the successful accumulation of research knowledge of sufficient depth to support a commercial undertaking. Industry-sponsored vaccine development represents the preparation and testing of candidate vaccines in large-scale Phase III clinical tests to prove safety and efficacy. This is accompanied by engineered scale-up to commercial production levels, submission and obtaining of product licenses, and development of distribution and sales. Such a degree of costly activities cannot be justified for products that do not have the clear scientific basis for safety and efficacy. In short, for industry to undertake product development, a scientific foundation for this undertaking must be provided by targeted development of basic research findings from investigator-initiated research.

Overview of the Current NIH Efforts on Targeted Vaccine Research

During the past decade, NIH funds for targeted vaccine research have supported the development of different approaches to AIDS vaccines and the development of animal models for testing candidate vaccines. (For the major ICDs participating in preclinical/targeted vaccine research and budgets, see Figure 2.) A number of different approaches to AIDS vaccines have been supported. These include peptide subunits of viral proteins, purified viral proteins, inactivated viral particles, recombinant viral and bacterial vectors expressing immunodeficiency virus proteins, plasmid DNAs expressing immunodeficiency virus proteins,

and live attenuated immunodeficiency viruses. A number of different animal models, with particular emphasis on nonhuman primates, have been developed to test the safety, immunogenicity, and efficacy of candidate vaccines: These use HIV-1 infections in chimpanzees; HIV-2 infections in baboons; and HIV-2, SIV, and SHIV (chimeras of HIV and SIV) infections in macaques. The NIH also has supported solicited research on particular problems in vaccinology, such as the use of adjuvants and induction of immune responses at mucosal surfaces. The primary and most important deficiencies in the program have been its failure to define broad spectrum antigens/epitopes, to achieve immune responses of appropriate quality (both humoral and cell-mediated) to provide protective immunity, and to achieve immunity with long-term memory at the mucosal site of infection. These are the principal hurdles for future research.

Figure 2. Financial Support and Coordination of NIH-Sponsored Targeted Vaccine Development.



Lack of Critical Coordination of NIH-Supported Targeted Research

To date, no overall coordination has been provided for NIH-supported targeted research. Current mechanisms for coordination of programs are Institute-specific. Even within an Institute, the level of coordination and oversight has been different for extramural and intramural initiatives. Overall, extramural programs (where researchers compete for support) have received the most oversight. For example, the Vaccine and Prevention Research Program (VPRP) of the DAIDS has provided coordination for extramural programs supported by the

NIAID, and these programs and their management have had intermittent oversight in the past by the NIAID Advisory Council as well as an external review group (Summary of the report to the NIAID Advisory Council provided to the Panel).

To a large extent, the lack of central coordination for the NIH-sponsored vaccine development effort reflects the historic role of the NIH in supporting investigator-initiated basic science research. Given the dwindling involvement of private industry, the lead responsibility in targeted vaccine initiatives will fall to the NIH. The Panel recommends that careful consideration be given as to how the funding structures of the NIH can be adapted for the effective accomplishment of targeted research.

2. Problems Confounding the Development of an AIDS Vaccine

Several major problems confound the development of an AIDS vaccine (Table 1). These include (1) the failure to have identified candidate vaccines that have a chance to be both safe and highly efficacious, (2) the confusion of preclinical trial results by the use of animal models with virus challenges that differ in virulence, (3) the lack of adequate sample size to definitively answer questions in trials in nonhuman primates, and (4) the failure to develop and implement tests for immunity that distinguish responses that are of substance for protection (correlates for protection).

a. Failure to Identify Candidate Vaccines With Perceived Safety and Efficacy

A number of different approaches to an AIDS vaccine have been tried. Discouragingly, none have resulted in the development of a clear candidate for an HIV vaccine. In monkey experiments, the most protective vaccines appear to be live-attenuated, genetically defective immunodeficiency viruses. Such live vaccines, however, are fraught with concerns for safety, such as the potential to cause cancer by insertional mutagenesis, the risk of disease in immunocompromised or immunologically immature (newborn) hosts, and the potential for regaining virulence by recombination in the recipient host. In contrast to the live-attenuated vaccines, the perceived safe vaccines (such as protein subunits) have shown little promise for protective efficacy. Furthermore, in most instances, evaluations of the perceived safe vaccines in animal models have been performed where the challenge virus was administered at the peak of the immune response after booster vaccinations, making it difficult to project how approaches that have protected or modified disease would translate into vaccines with long-term efficacy for heterologous infection. Finally, multicomponent vaccine strategies now being tested for safety and immunogenicity in humans have had limited opportunity for evaluation in animal models, which afford the opportunity to use viral challenges to assess protective efficacy.

Table 1. Problems Faced by NIH-Sponsored Targeted Research for AIDS Vaccines

1.	No clear choice as to which vaccine approaches or combination of vaccine approaches offer the most promise for both safety and efficacy.
2.	No one animal model in which vaccines are being tested. No clear certainty as to which of the nonhuman primate models best mimic human infections with HIV.

3.	Failure to identify the kinds of immune responses that provide correlates of protection. Confusion over role of correlates in different test models.
4.	Failure to define antigens/epitopes and adjuvants or optimal vectors to be used in a vaccine.
5.	Failure to achieve durable induction of protective immune responses (with memory) at mucosal sites.
6.	Failure to adequately develop models of maternal/infant transmission for testing vaccines in the newborn or pregnant animal.

b. Need for Comparative Testing of Candidate Vaccines in the Same Animal Models

Through NIH-sponsored investigator-initiated research, competing vaccine approaches have been evaluated in different animal models. Relatively little work has been done (or has been possible to do) to directly compare the efficacy of different vaccine approaches. Given that the independent trials have offered some hope for a vaccine, yet failed to provide a vaccine preparation that is clearly worthy of further pursuit, direct comparisons of different vaccine approaches must be undertaken to identify those that indeed offer the most promise. This will require centralized coordination of a targeted vaccine development effort and a transition from independent investigator-initiated trials to a venue of centralized coordination, evaluation, and problem solving.

c. Need for the Identification of Correlates of Protection

The development of an HIV/AIDS vaccine also has been hampered by the failure to identify immune responses that may provide a correlate for protective efficacy. The identification of correlates of protection is central to vaccine development. Such correlates provide a clear focus for the types of immune responses that must be raised by a candidate vaccine. The identification of correlates of protection would provide a strong justification for trials in humans. Existence of meaningful correlates also would provide a preliminary means for evaluating the success of vaccination in human trials.

The failure of investigator-initiated research to identify correlates of protection is due in part to the evaluation of candidate vaccines in different animal models. These animal model infections are inadequate because of the nonstandardized virulence of the challenge viruses (how long the infection takes to cause AIDS and/or death in test animals) and in the variable susceptibility of the challenge viruses to neutralizing antibody. Thus, immune responses, such as production of neutralizing antibody, that have correlated with protection in some challenge models (e.g., T cell tropic HIV in chimpanzees) have not correlated with protection in other models (e.g., SIV in macaques). This has led to immense confusion, since a relevant correlate for one vaccine model often has not proved a meaningful correlate in a model using a more vigorous challenge. Vaccine challenge studies also should include experiments to address the role of mucosal immune responses in the prevention of infection with SIV, HIV, or chimeric viruses and the potentiation of virus infectivity (enhancement).

d. Need for the Evaluation of Vaccine Approaches in More Than One Model

At present it is not clear which of the various nonhuman primate infections is the best surrogate of the HIV-1 and HIV-2 infections that occur in humans. As mentioned above, animal models differ in the virulence of the challenge infection and in the host response to that infection. These differences affect the outcomes of vaccine trials. In general, protection has been more easily achieved against relatively avirulent infections (in which disease occurs after several years) than for highly virulent infections in which disease occurs within the first year. Given the uncertainty about which animal model most closely represents the minimum predictor for success in human trials, it is important that vaccine approaches be evaluated in animal models of different virulence. Such systematic evaluations would provide a rational base for the decision as to which approaches (and eventually as to which models) are appropriate to making meaningful predictions for human vaccines.

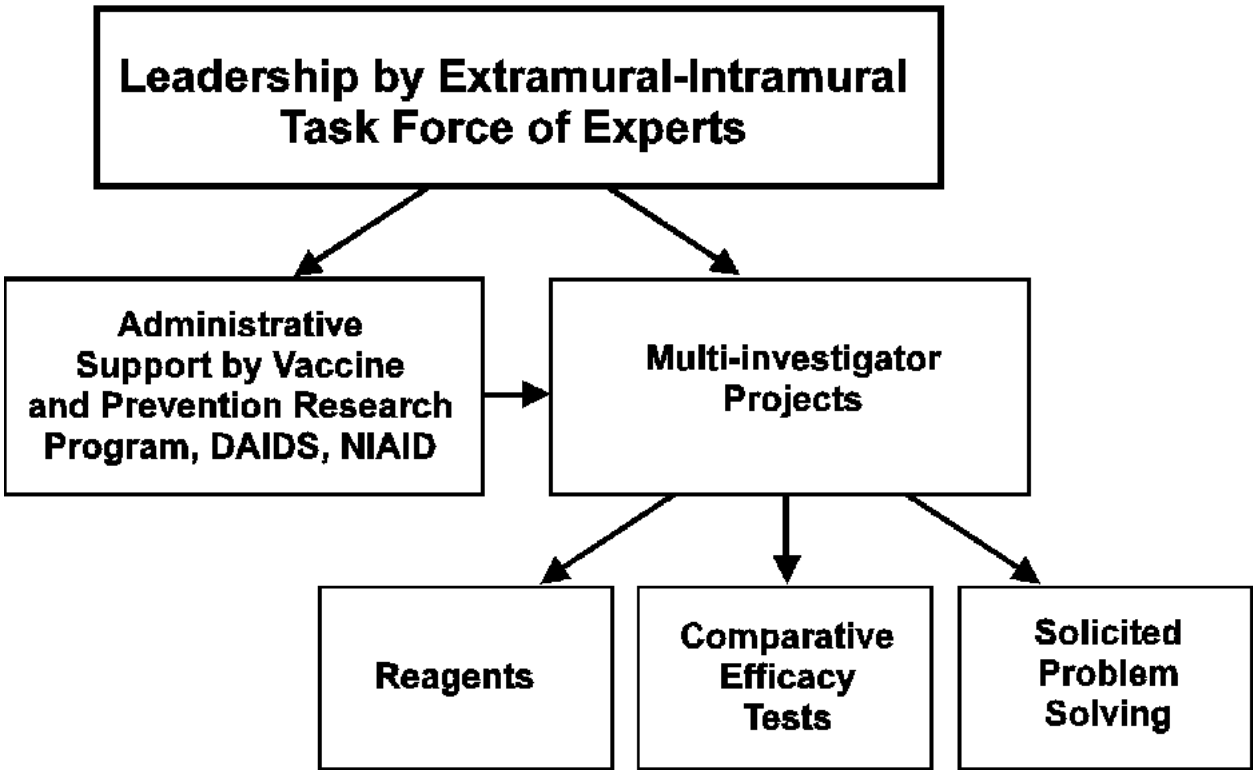
B. Recommendations

1. NIH should institute a mechanism for accomplishing targeted vaccine research.

Given that the NIH is the Federal Government's lead agency with the responsibility for developing an AIDS vaccine, it is essential that the NIH institute a mechanism for a targeted research program that will provide the missing link between basic research and the Phase I, II, and III clinical trials that lead to industrial development (See Figure 1). This will require centralized coordination of initiatives that are currently supported by different ICDs and by both extramural and intramural mechanisms. Centralized direction, review, analysis, and decision-making will be essential to sort out what is valid from that which is not valid in order to achieve progress from the multitude of approaches and models that have emerged from independent investigator-initiated projects.

The Panel considered various organizational structures that might support the achievement of targeted objectives by the NIH (see list at the end of this Subpanel report). The Panel decided that a mechanism that provides centralized leadership for independent projects by different investigators/organizations could combine the strengths and traditions of NIH-supported research with an effective program for targeted research (See below, Figure 3). The leadership of this group must be scientifically strong and constituted with authority for distribution and redistribution of funds between the ICDs within the NIH. The charge of this team might best be achieved if the targeted vaccine program were centered in a single ICD such as the NIAID.

Figure 3. Proposed Mechanism for the NIH to Accomplish Preclinical Targeted Research for AIDS Vaccines.



2. NIH should establish a team of extramural-intramural experts for centralized direction of HIV/AIDS targeted vaccine research.

The Panel recommends that an extramural-intramural team or task force be formed to review, define, and guide all NIH-sponsored efforts on targeted vaccine research (Figure 3). The team should be comprised of experts in vaccinology, in the immunology and pathogenesis of HIV-1, and in the commercial developmental process. This team would assume responsibility to set priorities and allocate resources in the area of targeted vaccine development. The primary goal of such an effort would be to evaluate, compare, and improve the vaccine approaches that have emerged from NIH-sponsored, investigator-initiated research to identify candidates for clinical trials.

Responsibilities of the team or task force:

- Provide coordination for preclinical vaccine trials by choosing vaccine approaches, antigens, desired immune responses, animal models, challenge strains, and assays for initial evaluation of candidate vaccines.
- Evaluate the results of comparative trials to identify those approaches and vaccine compositions or strategies that warrant further development.

- Identify correlates of protection for the purpose of evaluating each of the more promising approaches.
- Recommend contract research to solve problems that will overcome deficiencies in promising approaches.
- Ensure the rapid evaluation of promising new vaccine candidates or animal models to test vaccine concepts.

3. The NIH should provide additional funds for targeted vaccine development.

Given the importance of the development of an effective AIDS vaccine, it is recommended that additional funds be identified to provide a budget for the implementation of expanded vaccine efforts. These funds should be used to implement competitive contracts and solicited peer-reviewed research. It is estimated that a budget of $25 to $50 million per year would be necessary for the extramural-intramural team to achieve an effective multi-investigator targeted vaccine research effort. This allocation of funds should be exclusive of current support for basic science, clinical evaluation, and all other AIDS research and should be provided without diminution of current support for basic research programs.

4. Importance of establishing new funds for a new area of NIH activity.

The assumption of a major role in the targeted development of an HIV/AIDS vaccine represents an expanded, but critically important, activity for the NIH. This role is being undertaken because developing an HIV/AIDS vaccine has proved to be more complex than anticipated and still lacks the substantive scientific knowledge required for a realistic industrial effort. Because of the importance of protecting the Nation and potentially other areas of the world against the expansion of the AIDS epidemic, the budget for these activities needs to be provided from new funds, not from the redirection of funds from the traditional basic science program of the NIH, nor from the extramural funds currently categorized as "Basic AIDS Vaccine Research."

List of Supporting Materials

Hilleman, M.R., Whether and when an AIDS vaccine? *Nature Medicine* **1**:1126-1129, 1995.

Hilleman, M.R., Overview: Practical insights from comparative immunology and pathogenesis of AIDS, hepatitis B, and measles for developing an HIV vaccine. *Vaccine* **13**:1733-1740, 1995.

Report of the "Division of AIDS Ad Hoc Review of the AIDS Preclinical Vaccine Research," May 22-23, 1995. Scott Koenig, Chair. (Provided by NIAID)

III. Clinical Trials Research Subpanel

Introduction

Clinical trials research in the AIDS vaccine area encompasses several widely divergent scientific issues. To be successful, this endeavor must channel the efforts of a diverse group of experts: basic research scientists, clinicians, community representatives, company sponsors, statisticians, and epidemiologists in active functional networks. Because even small trials can require up to 2 years to complete, resources and energy have to be committed for extended periods of time by clinical staff and trial participants at evaluation units, with little likelihood of individual gain on the part of the volunteers. Therefore, tightly linked, preclinical research should be used to guide and support these efforts wherever this is rational and feasible. As safety and immunogenicity studies are expanded and populations at risk of HIV-1 exposure are included, issues of counselling, informed consent, accurate assessment of risk-taking behavior, and social harms become increasingly important.

A. Scientific Priorities: Opportunities, Needs, and Gaps

1. Scientific Issue from the FY 1998 NIH Plan for HIV-Related Research:

4.B The identification of viral antigens and vaccine delivery methods that elicit long-lasting protective immune responses against a broad range of HIV isolates will facilitate development of effective vaccines.

Status

The optimization of vaccine design and delivery requires increased collaboration among preclinical investigators, vaccine developers, and clinical trials groups. Such collaborations have begun to occur and are critical to continued progress.

Opportunities/Needs/Gaps

Tighter links should be forged between preclinical research in vaccine design, including the area of primate model testing, and clinical trials groups, so that findings in all areas rapidly stimulate improvements in vaccine candidates. Stronger links are specifically needed between contract programs, between Institutes, and between those programs and groups conducting HIV/AIDS vaccine trials outside of the NIH.

In addition to the need for continued testing of existing vaccine concepts, the Panel sees an opportunity for human clinical vaccine trial networks to contribute to an understanding of protective immunity by conducting comprehensive studies of the human immune response to vaccination and infection.

2. Scientific Issue from the FY 1998 NIH Plan for HIV-Related Research:

4.D Suitable candidate vaccines need to be selected and evaluated in Phase I and Phase II trials to determine safety and immunogenicity.

Status

Without better animal models that are predictive both of the immune responses observed in humans and of the impact of HIV candidate vaccines on disease development or clear correlates of immune protection, an empirical approach is necessary to evaluate candidate HIV vaccines in human Phase I and II trials.

To date, the NIAID AVEG clinical trials network has conducted Phase I trials for most of the currently available HIV vaccine products as well as a Phase II study of two recombinant envelope glycoprotein subunits (see Appendix A). Neither the AVEG nor other research groups have identified vaccine approaches that have progressed to efficacy trials.

Selection of vaccine candidates for Phase I and II testing operates smoothly through the Vaccine Selection Committee and the AVEG. Infrastructure and investigators are in place to continue to conduct clinical trials at current or higher levels of enrollment. Funding to six sites is committed for the next several years. (A 5-year cycle of funding was initiated in FY 1994 to the AVEG sites and for supporting and laboratory and statistical centers.)

Opportunities/Needs/Gaps

The primary gap identified by the Panel is the shortage of promising new candidate vaccines for human testing and the low level of commitment from private industry. This situation is not likely to change in the next several years.

There is, at present, no acknowledged process for developing HIV vaccine candidates that do not have the backing of private companies (although the capability theoretically exists either at FCRDC or through contract mechanisms for the NIH to produce small lots of vaccine for testing). This was identified as a need, particularly for small research groups.

Strategies not actively pursued by private industry have not been moved into human trials as rapidly as industry-sponsored products.

3. Scientific Issue from the FY 1998 NIH Plan for HIV-Related Research:

4.C Distinct study designs and vaccine or intervention strategies are needed to achieve protection of newborns and infants because of the unique nature of their immune responses and modes of exposure to HIV.

Status

Encouraged by the results of ACTG 076, which demonstrated the ability of AZT to significantly reduce HIV transmission from mother to infant, researchers continue to place a priority on developing methods to prevent transmission, especially for settings where long-term antiviral treatment may not be available.

Opportunities/Needs/Gaps

The probability that a proportion of maternal/infant HIV transmission occurs perinatally rather than *in utero* provides an opportunity for immunoprophylaxis of the infant or immunotherapy of the mother (see Appendix C).

Recent reports suggest that, in rare instances, infants may clear an initial infection. If additional such cases are identified, they might provide a unique opportunity to define protective immune responses to HIV, since clearance of infection would be one end point for a successful vaccine.

4. Scientific Issue from the FY 1998 NIH Plan for HIV-Related Research:

4.E Preparation for HIV vaccine efficacy trials requires characterization of the biological and behavioral factors in affected populations, including seroincidence, development of an infrastructure and a series of studies and planning activities to ensure trial feasibility.

Status

NIAID has established the HIV Network for efficacy trials (HIVNET), a network of domestic and international sites for trials of various strategies to prevent HIV infection, including but not limited to HIV vaccine candidates (see Appendix B).

Domestic and international HIVNET sites have succeeded in rapidly enrolling large numbers of high-risk individuals into cohorts for baseline studies. These sites subsequently have begun to gather data on risk and incidence of HIV infection, to assess willingness to participate in future vaccine trials, and to evaluate consent procedures.

Because of the current status of Phase I/II trials, randomized efficacy trials of alternative vaccine concepts could begin in the United States no earlier than 1998.

Trials of other prevention interventions have already begun at some of the international HIVNET sites. Several domestic HIVNET sites also have received funding and are currently developing protocols for non-vaccine prevention interventions, i.e., microbicide/barrier/STD and behavioral studies that would last 1 to 2 years.

Opportunities/Needs/Gaps

The HIVNET domestic and international sites, laboratory, and statistical center represent a substantial financial investment in HIV prevention and vaccine evaluation (see Appendix B).

The total AIDS research funding for the HIVNET in FY 1994 was $21.2 million, of which $16.6 million was coded as vaccine research (Infrastructure for Vaccine Efficacy Trials). This includes funding allocated early in FY 1994 to start up the Domestic Master Contract (DMC) and the International Master Contract (IMC) as well as the second portion allocated in late FY 1994 to fund a statistical center, the network's central laboratory, and the individual sites funded through the DMC and IMC, whose subcontracts were actually initiated in early FY 1995. The FY 1995 renewal funding was $16.5 million, of which only $3.66 million was identified as vaccine-related research, and a much larger portion of funding was coded as epidemiology and natural history.[*]

Some current HIVNET work, particularly in the United States, is now more accurately defined as epidemiology and natural history; its major focus has been preparation for evaluation of vaccine candidates to prevent HIV infection.

At present, the dilemma for NIAID is the potential for a gap in time between the completion of HIVNET baseline seroincidence studies and the availability of adequate data from Phase I/II studies of the next most likely vaccine candidates (or other prevention interventions) to be able to decide on their advancement to Phase III efficacy trials. If current vaccine candidates are not advanced, this gap may be substantial. If other non-vaccine interventions are advanced, it is not clear when or how vaccine candidates available at a somewhat later date can be advanced.

5. Scientific Issue from the FY 1998 NIH Plan for HIV-Related Research:

4.F Conduct HIV vaccine efficacy trials of the most promising candidate vaccines in well-characterized high-risk populations to identify effective vaccines for the control of HIV infection.

Status

The most promising vaccine concepts should be advanced to efficacy trials, if preliminary data justify doing so. It has not been determined how decisions will be made to advance candidate vaccines into Phase III, although NIAID has begun to define criteria for advancement of vaccine candidates on a product-by-product basis.

Opportunities/Needs/Gaps

Criteria for advancement of candidate HIV vaccines should be determined in advance. The decision-making process needs to be open, i.e., including participation of both the larger scientific and affected community, more clearly defined, with a specified person or group that has final decision-making authority.

Industry would prefer that criteria for selection of candidate vaccines for advancement to efficacy trials be determined beforehand.

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[*]This represents a shift of nearly $13 million or 10 percent of the NIH vaccine-related research category.

6. Scientific Issue:

Determine whether vaccines can play a role in post-infection treatment of HIV disease.

Status

In the past, the same HIV vaccine candidates designed for prevention have been placed into treatment trials. The rationale for such trials is that a new anti-HIV, vaccine-induced immune response would be cross-reactive with host virus and control the virus. A different type of effort is required to evaluate these and other immunogens in HIV-infected individuals.

After reviewing information available from current therapeutic vaccine trials, the Panel believes that therapeutic HIV vaccine trials should be considered strictly as part of AIDS therapeutics research, where they should compete against other immune-based, antiviral or combination therapies for funding.

Opportunities/Needs/Gaps

The Panel members seriously question the value of continued pursuit of a therapeutic approach with existing envelope vaccine candidates. The completion within the next year of several large, industry-sponsored, therapeutic vaccine trials in the United States, Canada, and Europe (including three NIH co-sponsored trials) and publication of the results should provide a more definitive picture of any potential benefit.

B. Review of Clinical Trials Vaccine Research at the NIH by Scientific Priorities

The Panel's primary concern is ensuring that a pipeline of promising vaccine approaches and products exists, while maintaining Phase I/II capability and readiness for eventual efficacy trial opportunities.

1. Identify Vaccine Components and Delivery Methods

Although vaccine candidates are largely identified through basic research and animal model studies, human Phase I and II trials play an important role in HIV vaccine design and development. *In vitro* assays and immune response data from animals are often more robust and may not reflect effective human immune responses to HIV vaccines. Standardization, improvement, and development of new assays for measuring immunogenicity should be priorities of the clinical trials networks.

When possible, efforts should be focused toward using clinical trial networks and cohorts to advance the overall knowledge about human immune response to different HIV vaccine strategies. In turn, this knowledge should be utilized to improve and refine vaccine design.

2. Select and Evaluate Candidate Vaccines in Phase I and Phase II Trials

Without better animal models or clear correlates of immune protection, an empirical approach is necessary to evaluate and advance the most promising vaccine concepts. By their very nature, human trials of candidate HIV vaccines will be more definitive, but also riskier and more expensive than other avenues of vaccine research. Extreme care must be taken to ensure safety, ethics, and scientifically sound clinical study designs. Both preclinical and clinical milestones should be developed that determine to what extent a candidate vaccine is advanced.

3. Explore Ways To Achieve Protection in Newborns and Infants

Domestic and international trials are in progress to evaluate envelope vaccines and the ability of human polyvalent anti-HIV immunoglobulin (HIVIG) products to prevent HIV-1 transmission from mother to infant. These studies may provide answers to important issues of immunity to genetic variants and advance the knowledge base for this line of research. (Note: In FY 1994, these studies were not coded as vaccines but as therapeutics.)

Trials of HIV vaccines in the infants born to HIV-infected mothers should be conducted independently of trials in other high-risk populations, because the risk of infection, even with AZT treatment, still exceeds that in most at-risk adult populations. This effort should be coordinated between NIAID and NICHD.

4. Prepare for HIV Vaccine Efficacy Trials

The amount of resources allocated for vaccine efficacy trials (through HIVNET, a few related R01s, and other contracts) seems high, as it is largely for vaccine preparedness, other prevention research, and infrastructure. However, ultimately it will be very valuable to establish such programs and maintain readiness for conducting successful efficacy trials. Funding levels should reflect prospects for use of the cohorts for multiple, investigator-initiated, high-value, high-quality investigations in line with the HIVNET mission to test efficacy of products and approaches to prevent HIV transmission. Recommendations for this relatively new program are outlined below.

5. Conduct HIV Vaccine Efficacy Trials

The relative importance of vaccine efficacy trials in relation to other vaccine objectives (understanding host defense mechanisms, developing new vaccine strategies, and protecting newborns) will change unpredictably with time, but is likely to move toward more emphasis on human trials as progress is made in other areas. New vaccines or encouraging results in early trials would require increases in funding or at least a substantial shift of resources from activities now being pursued in HIVNET in order to initiate and conduct vaccine efficacy trials.

6. Determine the Role of Vaccines in Treatment of HIV Disease

Ongoing trials are likely to determine whether current approaches in HIV vaccines have any promise for therapeutic treatment of HIV disease without further resources. Furthermore, if it is desirable to modify the immune response to shift the balance or the specificity of the immune response during HIV infection, distinct approaches, different from those taken for preventive HIV envelope candidate vaccines, probably will be required. Such approaches should be prioritized and pursued as part of a therapeutic agenda.

C. Review of Clinical Trials Vaccine Research at the NIH by ICD

National Institute of Allergy and Infectious Diseases (NIAID)

Of the $46.7 million expenditures designated in FY 1994 as AIDS vaccine clinical trials (OAR category 4C, $9.4 million) and development of cohorts and infrastructure for vaccine efficacy trials (4B, $27.3 million), 78 percent ($36.5 million) was managed through the DAIDS, NIAID. The bulk of this NIAID-sponsored effort is conducted through various extramural contracting mechanisms, with Research Management Support (RMS) accounting for 4.5 percent of the total. This concentration of these efforts in one Institute has led to the development of a more coherent and unified vaccine research program than found in other NIH AIDS research efforts. Nonetheless, several improvements can be made.

The caveat for this directed approach is that particular attention must be paid to accommodating alternative research approaches and incorporating peer review: both periodic program reviews and prospective review for studies begun after contracts are in place.

The Panel believes that NIAID should continue to direct all NIH HIV vaccine clinical testing, as long as their program is subject to regular input and objective thorough evaluation by non-Governmental extramural experts. Because of the relatively high cost of clinical trials and the need for comparative data, the structure of contract groups with common laboratories and data centers seems desirable. NIAID did not conduct intramural clinical trials for preventive vaccines in FY 1994 but has done so in the past. As with NCI intramural research (see below), the Panel recommends using existing extramural contract groups designated for this purpose whenever possible to avoid duplication of resources and to ensure comparability of analyses.

<u>Scientific Advances and Gaps</u>

Virtually all of the scientific advances and gaps described above in Section A, Status and Opportunities/Needs/Gaps, for vaccine clinical trials can be ascribed to NIAID.

Mechanisms

The bulk of NIAID's funding of vaccine clinical trials research including laboratory and statistical centers is through various extramural contracting mechanisms, primarily the AVEG and HIVNET, which are reviewed in greater detail in Appendices A and B. These two different networks differ in organizational aspects: The AVEG is a group of vaccine investigators on individual contracts administered directly by NIAID Program Staff. The HIVNET operates under two master contractors, in which the prime contract interaction is between Program Staff in NIAID and the principal investigators of the two Master Contracts. Distinct problems have arisen with lines of communication between investigators at subcontract sites, the linked statistical center contract, and Program Staff.

Funding

The primary program for conducting Phase I/II trials is the AVEG network and laboratories, which received 31 percent of the total vaccine clinical trials funds (OAR codes 4B and 4C, in FY 1994). Approximately 36 percent of the FY 1994 budget coded for vaccine clinical trials was allocated to HIVNET, and an additional 4.8 percent was encumbered by R01s, interagency agreements, and other contracts associated with vaccine field-site preparedness. The coding of the many and varied activities of vaccine trial preparedness and prevention interventions as "vaccine trials and infrastructure" overstates the amount supporting actual clinical trials. The FY 1996 NIH budget for AIDS research defines these scientific issues more clearly into prevention, epidemiology, and behavioral risk assessment, making the relative expenditures easier to compare and evaluate. Unfortunately these data were not complete and available for the Panel to review.

Vaccine trials to interrupt mother-to-infant transmission of HIV-1 have been conducted through the AVEG (vaccines) and the ACTG (therapeutics) networks. Together, with expenditures at the GCRCs (funded by NCRR) and the Centers for AIDS Research (CFARs) in FY 1994, these trials accounted for roughly $8 million of the total AIDS research budget.

Future Directions/New Initiatives Needed

The size and components of the AVEG and HIVNET groups should be as flexible as possible, so that the best resources are included, all available expertise inside and outside these programs is utilized, and unnecessary duplications of effort are eliminated. Continuity and long-term commitment are essential.

The Subpanel commends the Program Staff at the DAIDS for their management of these programs. However, the AVEG represents the vaccine clinical trials research activity of only a few researchers who focus on these projects. In the absence of vaccine candidates with proven efficacy, the wider research community must become involved in investigating human immune responses which would lead to more promising vaccine approaches and candidates. The time has come to engage other scientists with strong backgrounds in human immunology, HIV pathogenesis, and non-HIV vaccines in the HIV vaccine effort.

National Center for Research Resources (NCRR)

Non-NIAID expenditures for vaccine clinical trials (OAR category 4C) are predominantly through the NCRR General Clinical Research Centers (GCRCs) ($2.56 million).

Scientific Advances and Gaps

The Panel recognizes the flexibility and diversity of the national GCRCs and their ability to support local clinical research. AIDS vaccine research, including some Phase I studies of novel vectors, is being carried out effectively at some centers. In addition, training and access to GCRC facilities are being provided to some NIAID-sponsored programs, contracts, or grants. In FY 1994, several ACTG sites also were conducting therapeutic or pediatric vaccine trials.

Mechanisms

GCRC projects and utilization of an individual Center's funds are approved locally by Center review boards. During the review, the Panel found that NCRR staff are responsible for coding GCRC projects to specific AIDS research categories, and this coding is based on annual reports of patient visits which may not accurately reflect the level of a GCRC's support or resource allocation to ongoing programs or individual projects. Furthermore, this coding of projects to OAR scientific categories is done after the fact, delaying reporting up to an additional year.

Funding

Unfortunately, using the current information reporting system, it is virtually impossible to determine whether GCRC expenditures for clinical vaccine research areas are being allocated wisely or accurately at the sites to AIDS vaccine-related research.

Future Directions/New Initiatives Needed

OAR should require more accountability over the amount of AIDS funds going to GCRCs for project-related research, so that the level of expenditure accurately reflects contribution to the vaccine development effort.

NCRR should develop a more direct budget-tracking mechanism to justify the utilization of AIDS funds for clinical trials of HIV vaccine candidates or other training and infrastructure support. Furthermore, NCRR must audit reports of patient visits provided by the Centers to ensure the accuracy of the reports filed by the Center principal investigators.

National Cancer Institute (NCI)

At present, most NCI vaccine research is conducted by intramural scientists and is largely preclinical (see the previous two sections on Basic Vaccine Research and Development). However, one trial in HIV-infected individuals now is being conducted with a peptide vaccine.

Scientific Advances and Gaps

Basic researchers within NCI have developed several potential vaccine candidates but have chosen not to approach the Vaccine Selection Committee of NIAID and are proceeding to produce the product and evaluate their first vaccine candidates in clinical trials.

Mechanisms

In FY 1994, no NCI funds were ascribed to clinical vaccine trials, but NCI now is testing an HIV-1 peptide vaccine for safety in HIV-infected individuals, utilizing NCI intramural resources.

Future Directions/New Initiatives Needed

As NCI vaccine concepts reach the stage for testing in clinical trials for safety and efficacy, every effort should be made to advance them into existing NIAID clinical trial programs to avoid duplications of effort and to utilize mechanisms of external review and oversight already in place for this aspect of HIV/AIDS vaccine clinical trials. NCI is undergoing major organizational changes that may refocus its AIDS vaccine research effort significantly and address this problem.

For a better test of immunogenicity, the Panel recommends testing the vaccine candidates through the AVEG in low-risk HIV-uninfected volunteers rather than in HIV-infected subjects.

Fogarty International Center (FIC)

In FY 1994, the FIC supported a substantial portfolio ($8.85 million) of international infrastructure and epidemiological research training awards with AIDS research dollars. Of this sum, $6.82 million was defined as Infrastructure/Vaccine Clinical Trials (OAR research code 4B); this represents nearly 25 percent of all of the monies in this category and 6 percent of the total NIH budget for AIDS vaccine research. The remaining $2 million was assigned to OAR code 6A (Training); this represents over half of the total NIH budget for AIDS research training. This level of international training is appropriate, considering where the epidemic is having its greatest impact, but points up the unfortunately low priority placed on training in AIDS research in general.

Scientific Advances and Gaps

The FIC has the flexibility, through investigator-initiated projects in its AIDS International Training and Research Program (AITRP), to pursue areas of scientific research in AIDS important to vaccine research. Individual training fellowships allow scientists from international sites to acquire training, primarily in epidemiology but also in virology, immunology, or molecular biology in basic research or clinical laboratories in the United States.

Mechanisms

In FY 1994, the FIC funded 10 Individual Training Awards (F05, F06); 25 International Fellowships through its 11 AITRP (D43) awards for training and infrastructure in AIDS research; 9 International Postdoctoral Fellowships (T22) awarded to 4 centers; and 2 Fogarty Center Fellowships. The FIC also awarded 8 small grants (R03) designed to provide supplements to encourage established investigators to participate in international AIDS vaccine research studies.

Future Directions/New Initiatives Needed

The Panel raised serious concerns about the relative size of the budget for the FIC program compared with the overall NIH effort in AIDS vaccines and with the extraordinary amount of funds allocated to training relative to the entire AIDS training budget.

In many cases, the FIC AITRP awards appeared to be linked to NIAID-sponsored HIVNET sites and should be considered a formal part of these networks and reviewed accordingly.

The FIC should assess its training programs and focus them to truly fulfill the defined goals of assisting the AIDS vaccine research programs in developing countries. There is concern that, in some cases, the training programs are merely providing inexpensive help for highly technical HIV research activities of a few host institutions in the United States, research that cannot be readily utilized in the international site.

D. Special Issues

Funding mechanisms

NIAID

AVEG is funded through individual contracts with each participating unit, laboratory, and data center. The program is managed by DAIDS Program Staff and is largely self-directed by an executive committee of extramural investigators. This structure has worked well for a group this size.

HIVNET is funded through a Master Contract mechanism in which a private, non-Government organization is engaged to conduct contract functions that might ordinarily be undertaken by NIAID Program Staff. Two Master Contracts serve HIVNET: (1) the International Master Contract (IMC) for international sites and (2) the Domestic Master Contract (DMC) for domestic sites. One readily apparent consequence of the use of this mechanism is the absence of clear leadership of HIVNET. No single individual seems to have overall responsibility for the scientific direction of this program, especially for the domestic component, which, unlike international sites, has adopted a uniform study design applied to all sites.

Whether leadership eventually will emerge is not clear as yet. Thus, the Panel has serious questions about the Master Contract mechanism. Does this help or hinder the project? Does it dissipate leadership? Is it really needed? Is duplication of international and domestic contracts appropriate? The Master Contract mechanism for HIVNET appears to create layers and distance between NIAID Program Staff and the researchers at the sites that have not been conducive to rapid development of working arrangements.

Funding Issues in Other ICDs

As explained elsewhere in this report, the amount actually spent for vaccine clinical trials in FY 1994 is overstated as a result of inaccurate assignment of AIDS vaccine trials research codes to what appears to be epidemiology and natural history research. This was noted not only in the NIAID-sponsored HIVNET but also in the FIC AIDS epidemiology and training programs. In one case, the NCRR-supported GCRCs appear to have reported duplicate funding for research efforts supported by the NIAID-sponsored AVEG. In FY 1994 NICHD did not report any funding in the AIDS vaccine research categories, although it appears that vaccine trials research was conducted at some of the NICHD-funded pediatric clinical trial sites. In addition, some of the basic research in NICHD's grant portfolio should be reviewed for its relevance to HIV vaccines.

Peer Review

Because so much of the vaccine clinical trials program is funded through contracts, there is a constant need to be aware of and promote periodic peer review, both before and after significant projects are undertaken. The Panel sees the need to establish a broader base of investigators on peer-review panels to ensure adequate review and to identify opportunities to work creatively with collaborators outside the clinical trials networks to accomplish basic science and other research goals.

Cross-Institute and Interagency Collaborations

Through interagency agreements, NIAID has incorporated expertise from NIDA, FIC, the CDC, the U.S. Department of Energy, and the U.S. Department of Veterans Affairs into its vaccine development program. This effort seems altogether appropriate if NIAID is to spearhead the development of vaccines and related prevention research, which necessarily involves areas outside its primary expertise.

Cross-Disciplinary Research: Overlaps With Other Panels

The HIVNET program bridges several disciplines, especially vaccines, epidemiology, and prevention. Thus it transcends the individual purview of several Area Review Panels. It is desirable for large programs to make scientific contributions across several areas; however, difficulties arise when appropriate expertise is not available or efforts duplicate other programs. Therefore, it is important for DAIDS to collaborate with and to incorporate expertise from other programs in planning its prevention agenda in general and in any nonvaccine efforts it pursues.

Links Among Research, Services, and Communities

Two specific points related to communities potentially involved in HIV/AIDS vaccine research require attention: (1) transfer and exchange of research findings and provider and community concerns and (2) participation of community representatives in AIDS research activities. NIAID has been a pioneer in involving communities in its research programs through open scientific meetings, local and national Community Advisory Boards, and the inclusion of representatives from the affected community on peer-review panels at all levels. This effort has been of benefit to all parties and to AIDS research programs as a whole. The Panel commends NIAID for these actions.

However, a great deal more must be done to involve the public in the difficult processes and decisions that face development of an AIDS vaccine. Significantly more attention and resources should be devoted to educating communities that will participate in trials.

Links Between the Public and Private Sectors

NIAID has brought companies together as collaborators through the NCVDG and for particular AVEG trials, e.g., a trial of avipox HIV vaccine vectors (Pasteur-Merieux Connaught and Virogenetics) plus envelope subunit boost (Chiron). This model should be strongly encouraged as a particular role for Government in a public health crisis.

The Panel was provided with an overview of the Department of Defense (DoD) AIDS vaccine effort by staff of the Walter Reed Army Institute of Research (WRAIR). The Panel supports the DoD's highly focused and coherent research effort on preventive vaccines and encourages WRAIR and DAIDS staff to continue to work together on strategies for investigating newer vaccine approaches to evoke antibodies to conformational cross-strain determinants that may be needed, especially in the international vaccine effort.

Dr. Seth Berkley of the Rockefeller Foundation provided the Panel with an overview of the newly established International AIDS Vaccine Initiative (IAVI). The stated goal of this new initiative is to quicken the pace of vaccine development so that a vaccine suitable for use throughout the world becomes a reality. The intent is to support research and development activities on vaccine concepts not being pursued by industry by working with Government, private industry, funding groups, and regulatory authorities to create a more favorable environment that will encourage increased investment in HIV vaccine research and development. If adequately supported by new independent funds, this effort should enlarge the intellectual and financial investment in the development of vaccine candidates.

Poor economic incentives for vaccine development appear to be an obstacle for industry involvement at many levels. As a high priority, OAR should invest resources to analyze options and propose solutions for this problem.

Access and Ownership of the Products of NIH-Supported AIDS Research

It may be time to consider cooperative or public ownership arrangements for AIDS vaccine products, especially for riskier approaches, since private industry has largely been reluctant to enter this area at levels required if there is to be an active program.

E. Conclusions and Recommendations

The many challenges for developing HIV vaccines have created a tension over what resources should be devoted to efforts to understand more about the basic biology of the virus (i.e., immune responses to HIV through *in vitro* studies, animal models, and studies of both chronically infected individuals who have controlled viral load as well as multiply-exposed, uninfected individuals) and what resources should be allocated to clinical studies to evaluate candidate vaccines in human subjects.

Some scientists have voiced the opinion that no human clinical efficacy trials are justified until more is understood about the virus. Others have argued that some questions, such as identification of the correlates of immune protection, may be answered only in human clinical trials in populations at high-risk for exposure to HIV-1 once protection can be demonstrated. Most scientists have taken an intermediate position.

The NIAID position has been to undertake both basic and empirical research, since success with either approach alone cannot be predicted. The Panel concurs with this view, because it has become evident that the predictive value of animal studies has its limitations. Further, HIV/AIDS vaccine candidates can be tested effectively and safely in low- and high-risk populations. Finally, the information gathered on comparative immunogenicity and safety of individual candidate vaccines evaluated in Phase I/II clinical trials will be essential to determine future directions for vaccine development.

The capability to do clinical trials of AIDS vaccines in humans must remain a high priority. Given uncertainties about mechanisms of immune protection, studies must be designed to gather samples that could be used in ancillary studies to answer fundamental scientific questions and help direct future vaccine development. However, NIAID needs to promptly develop concrete plans and timelines for making decisions about whether and when to launch efficacy trials. Such plans will help ensure that clinical trials networks are effectively utilized or downsized or redirected to other prevention or risk intervention research if appropriate vaccine strategies do not become available.

Key Recommendations for HIV/AIDS Vaccine Clinical Trials Research

The poor economic prospects for vaccine development appear to be a restraining force on the entire vaccine development effort.

- **OAR, as a high priority, should invest resources in analyzing and proposing solutions to this problem. It may need to attract more industrial-sector participation or consider cooperative or public ownership arrangements for AIDS vaccine products, especially for riskier approaches.**

Tighter links must be forged among basic research efforts, animal studies, vaccine developers, and clinical trials groups. Because clinical trials are conducted largely through contracted programs, the Panel sees the potential danger of NIH/NIAID clinical programs missing opportunities to work creatively with new or outside collaborators.

- **It is essential that AVEG and DAIDS Program Staff establish a mechanism to allow scientists to request collaboration with contracted programs for studies with clinical samples, with some funds set aside to support such collaborations.**

Criteria for selection of candidate vaccines for advancement to efficacy trials have appeared to some to be arbitrary and influenced by small "inside" groups of investigators.

- **Criteria for advancement of candidate HIV vaccines should be determined in advance. The decision-making process must be open (i.e., including participation of both the larger scientific and affected community), more clearly defined, and with a specified person or group that has final decision-making authority.**

Efficacy cannot be predicted for preventive HIV vaccines, and it seems unlikely that the first ones tested will be highly effective.

- **Therefore, new Phase I and Phase II trials should continue to be a high priority even if one or more vaccines advance into efficacy trials.**

Given the OAR mandate to allocate funds for specific scientific priorities, the Panel finds it difficult to accept that the amounts coded by ICDs for vaccine clinical trials are actually supporting such trials, directly or indirectly. Both coding systems, by Functional Category (Mason Code) and by NIH Scientific Objective, are subject to miscoding through mistakes and inconsistencies in interpretation by ICDs. Accuracy of coding is essential for OAR to influence research direction.

- **OAR should develop a process to assist with and review the allocation of resources and coding of projects in the AIDS budget.**

The major impact of HIV/AIDS is not in the developed world, but on developing countries. Important vaccine research is now being carried out worldwide, and a vaccine must be available to the developing world.

- **NIH should retain the commitment to international trials and scientific collaborations, given the global nature of this disease.**

Recommendations for Specific ICDs
(For more details and recommendations, also see Appendices A and B.)

NIAID

The Panel sees great opportunities for the existing human trials networks to conduct laboratory-based human immunology studies that could contribute to an understanding of protective immune response, response to vaccination, and infection.

- **Significant resources should be directed toward using clinical trial networks (AVEG and HIVNET cohorts) to advance our overall knowledge of the immune responses to vaccine strategies.**

- **Laboratories linked to the clinical trials effort should focus on automation of routine assays, development and validation of new and better assays, and more comprehensive studies of the human immune responses to vaccination. It is particularly important that methods to quantify cellular responses, especially CTL, be encouraged.**

- **NIAID should streamline mechanisms for ensuring access to specimens for investigators outside of AVEG/HIVNET and ensuring available funding for specialized studies.**

- **NIAID should be more active in seeking out and assisting in the production of pilot lots of vaccine candidates, if needed, to test new vaccine strategies.**

- **NIAID should dedicate additional personnel or resources to facilitate the trials "start up" process (protocol development, satisfying FDA requirements, filing investigational new drug [IND] applications, making arrangements with manufacturers) to enter candidate vaccines into Phase I/II trials and ensure effective use of the AVEG trials network**

The Panel's extensive discussions of the HIVNET program and the many uncertainties in the timing of vaccine development led to the following series of recommendations:

- **NIAID should establish a rigorous plan and schedule for deciding the future direction of HIVNET as soon as possible. HIVNET, or selected components, should be decreased in scope or eliminated after baseline studies are completed, unless clearly appropriate vaccine or nonvaccine intervention trials are undertaken or anticipated in the near future.**

It will remain important to maintain a presence in and commitment to the participating communities for future vaccine trials.

- **More of HIVNET's resources should be devoted to educating communities that will eventually participate in trials.**

HIVNET investigators now have assessed the willingness of participants at risk for infection in their cohorts to volunteer in vaccine trials. Valuable trials experience would be gained by the sites if smaller trials were run in preparation for larger trials.

- **HIVNET should participate in expanded Phase II studies of HIV vaccines, especially when such trials involve people at some risk of HIV infection.**

HIV-infected individuals identified through HIVNET provide an important human resource for understanding the dynamics of the earliest stages of HIV infection.

- **Options should be developed to allow individuals to enroll in studies of the clinical benefit of early treatment, especially if the scope of such studies are expanded to include people with documented recent infections who are already antibody positive.**

The Master Contract mechanism may be complicating the ability of NIAID to manage its HIVNET program.

- **NIAID should exert closer oversight of HIVNET and the Master Contract mechanisms and initiate regular reevaluation of the funding mechanisms and funding level as changes in vaccine development plans occur.**

- **A reasonable percentage of the cost of HIVNET should be coded for clinical vaccine trial preparedness. The rest of the cost must be justified by the strength of the other research and coded appropriately under objectives in the annual NIH Plan for HIV-Related Research. (This issue has been addressed in FY 1995. See Appendix 2 on Coding of HIV Vaccine Resources.)**

- **Trials of HIV vaccines in the infants born to HIV-infected mothers should be conducted independently of trials in other high-risk populations, because the risk of infection, even with AZT treatment, still exceeds that in most at-risk adult populations.**

NIAID should establish a strong link between AVEG and HIVNET. Consideration should be given to possibly merging the two efforts.

- **NIAID should explore ways that bring AVEG and HIVNET together that build on the strengths of each group and facilitate sharing of knowledge and skills.**

- **NIAID should consider if and how its intramural program can contribute to the clinical vaccine development effort. This effort should be coordinated with the extramural AVEG efforts.**

<u>NCI</u>

- **As NCI vaccine concepts reach the stage for testing in clinical trials for safety and immunogenicity, every effort should be made to advance them into existing NIAID Phase I/II trial programs to avoid duplication of resources and effort.**

NCRR

With its current monitoring system, it is virtually impossible for NCRR to accurately determine whether GCRC expenditures are being allocated wisely or accurately to AIDS vaccine-related research.

- **NCRR and OAR should work together to develop a mechanism for direct budgeting and tracking of AIDS research funds allocated to vaccine clinical trials.**

FIC

- **A substantial proportion of the budget assigned to AIDS vaccine clinical trials infrastructure and AIDS training requires reexamination. FIC and OAR should work together to ensure that assignment of codes for vaccine clinical trials is appropriately applied.**

F. Reports for the Clinical Trials Subpanel

Appendix A: NIAID AIDS Vaccine Evaluation Group (AVEG)

[Note: The Subpanel did not review the AVEG directly, but relied on a recent review by an ad hoc panel of extramural scientists, presentations from NIAID, summary information, as well as trial synopses provided by DAIDS Program Staff and the experience of Panel members, some of whom receive funding from this program.]

In the AVEG, NIAID has put in place a well-coordinated and funded group of clinically oriented AIDS vaccine evaluation units (AVEUs). The AVEG consists of six AVEUs, each with some laboratory capability on site. There is one central immunology laboratory (CIL) at Duke University that performs routine assessments for all trials. In addition, there is one specialized laboratory for mucosal immunity at the University of Alabama and a centralized data center, the EMMES Corp., Potomac, MD. This combination of dispersed clinical sites and centralized analysis components allows for efficiency and flexibility.

The mission of AVEG is to evaluate promising candidate HIV-1 vaccines in Phase I/II trials. To this end, it is charged with:

- Testing strategies that represent the range of options available (i.e., subunits, peptides, live vectors, etc.).
- Carrying out a comprehensive evaluation of the safety of each approach.
- Assessing the humoral and cellular immune responses induced by each candidate vaccine using state-of-the-art assays.
- Facilitating further studies of each candidate vaccine by making specimens, etc., available to qualified investigators outside of this program who have interesting and scientifically sound proposals.
- Providing the information, obtained in Phase I/II trials, that is necessary for making decisions regarding the advancement of strategies to Phase III efficacy trials.

The Panel concurs with the conclusions of the recent external review conducted by NIAID and believes that the AVEG is functioning well and has been able to test most of the currently available HIV vaccine strategies. Approaches that have been tested by AVEG include the following:

- Recombinant envelope glycoprotein subunits produced in various expression systems (yeast, baculovirus, CHO cells, vaccinia) ranging from nonglycosylated denatured polypeptides to fully glycosylated native proteins.

- Envelope glycoprotein subunits combined with novel adjuvants.

- Genetically engineered pox virus vectors (vaccinia, avipox) expressing HIV envelope as well as other HIV-1 gene products.

- Various peptides and complex peptide constructs and formulations.

- Combination strategies consisting of priming with genetically engineered pox viruses and boosting with subunits (Vaccinia env + rgp120 subunit; avipox env + rgp120 subunit; and others).

- Virus-like particles.

AVEG has been successful in the recruitment and retention of both low-risk and high-risk volunteers. It has active Community Advisory Boards (CABs) at each site and a national CAB that includes a representative from the HIV-affected community on its Executive Committee. Particular efforts have been made to improve minority recruitment at every site and to create opportunities for younger clinical and basic research investigators.

To date, the full potential of the AVEG has been hampered by a shortage of candidate vaccines. The AVEG has the capacity to evaluate a larger number of candidate vaccines with little or no additional manpower, but it probably does not have capacity to do more than one Phase II study at a time without additional resources.

A considerable effort has been devoted to laboratory assessment of immune responses of vaccinees. Approximately 10 percent of the AVEG budget supports the CIL activities at Duke. Additional resources are allocated at each of the AVEUs for laboratory assessments; this is estimated to represent 20 percent of the AVEG site budget. However, the Panel felt that an even greater proportion of AVEG resources should be devoted to analyzing the consequences of immunization, even if this necessitates smaller members of individuals studied within Phase I/II trials.

The CIL performs a wide variety of routine immunologic assessments, including various ELISAs to assess antibody responses to the candidate vaccine; neutralization assays; and, on a more limited basis, lymphoproliferation assessments and CTL assays. The laboratory evaluation historically has focused heavily on assessments of humoral immunity because of difficulties in measuring CTL responses, and the nature of the candidate vaccines evaluated (envelope and subunit). More CTL assays are being done presently, especially with pox vector vaccines. Studies quantifying CTLs and assessment of nonenvelope CTLs are ongoing.

Consensus protocols exist for cell-mediated immunity assays performed in the central laboratory and at individual AVEU sites. Additional exploratory and ancillary studies are performed at the sites or at other laboratories; these are of value, but all data should be reported to the central database to avoid nonuniformity and for quality control. The capability of doing routine immunologic assessment does not appear to be limited, as the group is discovering that

more selective sampling may give an accurate picture of a particular vaccine candidate once the basic pattern of the immune response is established.

Because there is no clear-cut correlate of immunity to measure, the Panel believes that there should be a more concerted effort by the CIL to broaden studies of immune responses. Therefore, the relative emphasis on immunological analysis of vaccine candidates might best be shifted from a large-scale effort using traditional assays that catalogue the magnitude of humoral and cellular immune response toward more focused, comprehensive studies of human immune response to vaccination. Examples of such immunity studies would be studies of the balance between TH1 and TH2 responses, the role of CD8 cells in suppressing HIV replication, and the roles of antibodies and cells involved in viral clearance or viral dissemination.

Research Opportunities

Clinical trials of HIV/AIDS candidate vaccines provide a unique opportunity to study the response of the human immune system to HIV gene products. Since correlates of immunity to HIV infection remain undefined, it is not possible to select one form of immunity (e.g., humoral, cellular, mucosal) over another or to focus on traditional functional immune responses (e.g., neutralizing antibodies, CTLs) in order to characterize the immunogenicity or likelihood of efficacy of a particular vaccine candidate.

The CIL spends much of its effort manually performing routine assays. Automation of these assays, if possible, would free up human resources. More emphasis and resources should be placed on the development and validation of assays to assess cell-mediated immunity. It is particularly important that methods to quantify cellular responses, especially CTLs, be encouraged.

The Panel felt that the development of assays to assess mucosal immunity was adequately covered by the central Mucosal Immunity Laboratory (MIL) and the CMIGs. However, when these assays move into large-scale use, shifting of resources may be required.

The AVEG has sometimes taken unexpectedly long to move concepts/products into trials. More effort should be dedicated to streamlining the trial protocol development process so the trials network can be utilized more effectively.

Specimens

The specimens generated by the AVEG during the course of vaccine trials represent an extremely valuable resource. When appropriate, research projects beyond the scope of the initial trial utilizing these materials should be encouraged and funded. AVEG has been cooperative with outside investigators interested in obtaining specimens for their research. They have also been sensitive to the needs of the industry sponsors. However, the procedure for obtaining specimens also should be streamlined. The bureaucracy is still cumbersome, and it often takes considerable time to obtain approval and receive the materials.

General Conclusions

The clinical evaluation of candidate vaccines is the end of a pipeline. AVEG is currently suffering from a thin base of new products and strategies to feed this pipeline.

If new vaccine concepts and approaches do not generate candidate HIV vaccines, it will be difficult to justify sustaining AVEG at its current funding level. Industry involvement in AIDS vaccine development has been rapidly declining. However several concepts from small groups of investigators using DNA vaccines and other vectors have been moving toward clinical trials. Strategies for keeping industry involved need to be developed. In addition, NIAID should be even more active in seeking out and assisting both industry or academic investigators in the production of pilot lots of new candidate vaccines for testing in "proof of concept" trials in the AVEG.

Appendix B: NIAID HIV Vaccine Efficacy Trials Network (HIVNET)

[Note: The Panel did not review the effectiveness of HIVNET directly, since it is a new program. It relied on presentations from NIAID Program Staff; documents provided by NIAID, including the RFP and summary information provided to the Panel; and the experience of panel members, some of whom receive funding from this program.]

In 1993 and 1994, NIAID established HIVNET, a network of domestic and international sites for trials of various strategies to prevent HIV infection, including HIV vaccines, through two Master Contracts and as a solicitation for proposals from individual study sites. The overall objective of HIVNET was to create the infrastructure and gather baseline data to assess the feasibility and design of future efficacy trials in high-risk uninfected individuals and, eventually, to conduct trials of preventive HIV vaccines and other appropriate interventions to prevent HIV transmission. (Because of the perceived urgency in early FY 1994, this effort was "jump started" with supplements to several unsolicited R01 grants already funded by NIDA or NIAID and two interagency agreements with the CDC and the VA. These sites were required to compete with other sites for funding through the Master Contractor.)

Master Contractors were funded in late 1993 (FY 1994), and the associated Statistical Center, Laboratory Contract, and Specimen Repository were funded early in 1994. Proposals for domestic and international sites were received in early 1994, and domestic and international sites were funded in August-October 1994 (with a second allocation of funds to the master contractors in September 1994, i.e., also FY 1994). Altogether, eight domestic contracts (one each in San Francisco, Seattle, Denver, Chicago, Boston, and Philadelphia, and two in New York City) were funded for studies of homosexual men, injection drug users (IDUs), and women at high risk through heterosexual contact. Internationally, nine sites were funded (in Thailand, India, Uganda, Malawi, Kenya, Zimbabwe, Haiti, Senegal, and Brazil) for studies in high-risk adults and in infants born to HIV-infected women.

Since that time, domestic and international HIVNET studies have succeeded in rapidly enrolling large numbers of high-risk individuals into cohorts for baseline studies and have begun to gather data on risk and incidence of HIV infection and to assess the willingness of enrolled subjects to participate in future vaccine efficacy trials and to evaluate informed consent procedures.

NIAID's AIDS Research Advisory Committee (ARAC) recommended in June 1994 that large-scale efficacy trials of recombinant gp120 vaccines (those most advanced in testing at the time) be put "on hold" in the United States. This presented HIVNET, especially the domestic component, with the dilemma of potentially preparing for a vaccine efficacy trial when no vaccine candidate was likely to be available for several years.

In contrast to the NIAID ARAC recommendation, a World Health Organization (WHO) committee recommended that efficacy trials of gp120 vaccines could be conducted in countries where the incidence of HIV infection has been found to be extraordinarily high, where other interventions either have been ineffective or could not be applied, and where the local

government endorsed the trial. Investigators at one of the HIVNET international sites (Thailand) are participating with the DoD in its Phase I/II studies of gp120 vaccine matching the local HIV clades.

The HIVNET Laboratory Contract functions differently from some of the major laboratories under other NIAID contracts. Its task is to do assays that can be performed on a large scale on specimens from large numbers of participants, rather than the labor-intensive assays required of other laboratories focused more on detailed immunological assessments or pathogenesis. Thus, the emphasis is on use of standard assays to detect HIV and immune response to the virus, quantitation of virus in infected participants, and broad identification of HIV variants seen in HIVNET populations that would help target appropriate vaccine candidates.

Clinical Trials

Trials of nonvaccine interventions to prevent HIV infection have already begun at some of the international sites. Although proposals for the domestic HIVNET sites included plans for nonvaccine trials after the baseline studies, NIAID has not committed to funding such trials until recently. The current commitment to domestic HIVNET sites for the completion of baseline studies in preparation for vaccine efficacy trials ends in 1997. The international HIVNET sites that already are conducting other nonvaccine interventions have commitments for funding to complete the currently approved trials.

From the outset, several international HIVNET sites proposed to undertake trials assessing the efficacy of nonvaccine interventions while gathering baseline data for eventual vaccine trial design:

1. A clinical efficacy trial of HIV immune globulin (HIVIG) for newborns is being planned in Haiti.
2. A trial of vaginal cleansing to prevent maternal/infant transmission was conducted in Malawi and is being modified to assess the efficacy of vitamin A treatment of the mothers.
3. Sex workers in Kenya are participating in Phase II/III trials of low-dose nonoxynol-9 as a topical microbicide to prevent HIV transmission.
4. A randomized trial of peer counseling to reduce risk behavior is being carried out in Zimbabwe.

Recently, additional funds have been allocated ($7 million) for the international and domestic HIVNET to carry out pilot studies of trials of nonvaccine interventions in 1996 and 1997. Proposals include evaluation of topical microbicides to prevent sexual transmission, an antiviral trial to prevent perinatal transmission, a trial of the efficacy of prophylaxis of other STDs on the incidence of HIV infection, behavioral interventions, and computer reporting of risk behavior. These trials of specific nonvaccine interventions are being designed and selected after the contracts are in place, so they would benefit from high-quality, critical peer review of their value and design. Most of these nonvaccine studies have been reviewed by the Natural History, Epidemiology, and Biomedical Prevention Research ARP or the Behavioral, Social Science, and Prevention Research ARP (see Cross-Disciplinary Research: Overlaps with Other Panels).

Intermediate-Sized Efficacy Trials

A Workshop on Alternative Trial Design, sponsored by AVEG, HIVNET, and NIAID, held in April 1995, concluded that trials in populations with an incidence of HIV infection as low as 2 percent per year (the incidence currently seen in the highest risk U.S. populations) could determine whether a vaccine (or some other intervention) was "reasonably" effective (i.e., had 60 percent efficacy or greater) or not (i.e., less than 30 percent efficacy), with prevention of HIV infection as the primary end point using a sample size as low as 1,500 per arm of the study. Prior considerations of study design had estimated a need for 3,000 participants per arm to estimate efficacy with a precision of ± 10 percent.

Additionally, based on data on the spectrum of immune responses to candidate vaccines, a study of this size also would be sufficient to determine whether a difference as small as two-fold in the level of vaccine-induced immune responses (which occurred in greater than 80 percent of the vaccinees) can predict protection against HIV in vaccinated individuals. Only if CTLs are detected in a larger fraction of vaccinees with the newer HIV candidate vaccines will it be possible for intermediate-sized efficacy trials to establish CTL levels as a correlate of protection.

Trials in populations with an incidence substantially higher than the 2 percent (discussed in the Workshop) would require an even smaller sample size to determine efficacy with the same precision. Thus, trials with vaccines having a limited expectation of efficacy might be most practically carried out among high-risk populations in certain international settings.

An advantage of conducting trials in domestic populations, however, is the relative ease of collecting, processing, and testing the kinds of specimens necessary to evaluate potential correlates of protection (especially cellular immune responses), information critical to future vaccine development if the first vaccines tested do not work or are only partially effective.

At the time of this review, at least one live recombinant vaccine (based on insertion of one or more HIV genes into an avipox virus capable of infecting human cells but not replicating) together with an envelope subunit vaccine was under consideration for human Phase II testing by the AVEG. One potential advantage of the avipox vaccine (possibly used as a priming vaccination with a gp120 boost) is induction of cellular immune responses in some vaccine recipients.

If study results indicate that it would be appropriate to test the efficacy of these vaccines against HIV infection, the earliest that randomized trials of such alternative vaccine concepts could begin in the United States is 1998. To meet this schedule, innovative ways of planning and conducting Phase II trials must be developed.

Recommendations

With the above considerations, the Subpanel recommends the following:

- **NIAID should establish a rigorous plan and schedule for deciding the future direction of HIVNET as soon as possible, including consideration of which candidate vaccines may be adequately tested to be considered for Phase III efficacy trials through the current HIVNET mechanism and the clear criteria for making that decision.**

- **HIVNET proposals for trials of the efficacy of nonvaccine interventions that have not undergone peer review or have been reviewed only by contract-associated review groups should be reviewed by an outside panel of experts to determine their quality and relevance to the field of HIV prevention.**

- **Collaboration with investigators in other fields of HIV prevention should be sought when studies beyond the current HIVNET expertise are undertaken. If, for example, efficacy trials of behavioral interventions are proposed, collaboration with behavioral scientists would be essential for such efforts. Dual support between NIAID and other relevant Institutes also might be appropriate in such cases.**

- **The potentially competing objectives (vaccine and nonvaccine trials for prevention of HIV transmission) must be carefully coordinated so that the ability to carry out HIV vaccine efficacy trials is not jeopardized once the opportunity and need for them arises.**

- **To ensure smooth coordination of the entire clinical vaccine trials effort, NIAID should establish a strong link between AVEG and HIVNET, possibly even merging the two efforts to minimize duplication and competition. Mutual representation on Steering Committees might be considered as well as collaboration between Central Laboratories. HIVNET also might be included in expanded Phase II studies of HIV candidate vaccines, especially when such trials involve individuals at risk of HIV infection. HIVNET has ready access to high-risk populations and involvement in such studies would help prepare the investigators and their communities for future efficacy trials.**

- **HIVNET, or selected components, should be eliminated or decreased in scope after baseline studies are completed, if no clearly appropriate vaccine or nonvaccine intervention trials are contemplated in the near future. However, it would be important to maintain a presence in and commitment to the participating communities for future vaccine trials. NIAID should consider mechanisms and activities for achieving this goal.**

- **NIAID should establish means to link HIVNET with non-HIVNET investigators so that resources generated by HIVNET efforts can be quickly and effectively utilized toward advancing the vaccine effort. For example, HIVNET studies will detect a relatively large number of early HIV infections during its baseline studies. Specimens from such cases could be used for more detailed investigation of HIV variants and pathogenesis to supplement HIVNET objectives, without unnecessary duplication. Additionally, HIV infections identified through HIVNET could provide an important**

human resource for trials evaluating the impact of early treatment of HIV infection, especially if the scope of such trials were expanded to include people with documented recent infections who are already antibody positive.

- **NIAID should clearly identify what proportion of the HIVNET cost is related to HIV vaccine development and evaluation and what would be better assigned to other areas of AIDS research, such as epidemiology, pathogenesis, and biomedical or behavioral nonvaccine prevention. FY 1994 coding of HIVNET as nearly all vaccine-related misleads both by exaggerating the vaccine effort and by underrepresenting HIVNET's contribution to other areas of epidemiology and prevention research.**

Appendix C: HIV Vaccine Trials in Newborns

Infants born to HIV-infected women must almost certainly be exposed to substantial amounts of virus *in utero* across the placenta and during delivery with exposure to maternal blood and body fluids. Yet only about one of four of these infants become infected, and this number can be reduced to less than 10 percent by the use of AZT. Results of the clinical trial ACTG 076 demonstrated that treatment of the mother and infant with AZT reduced HIV mother-to-infant transmission from 24 percent to 8 percent. Despite this success, reducing maternal-infant transmission remains a high priority, because even at the reduced level, HIV transmission exceeds that observed in most other high-risk populations. The probability that a high proportion of maternal-infant HIV transmission occurs perinatally rather than *in utero* provides a strong rationale for using immunoprophylaxis with antibodies or vaccines, even if begun postexposure at the time of birth. Recent preliminary data with passive antibody in infant or juvenile macaques support the continued interest in research in this area. Finally, in settings where extended antiviral treatment may not be applicable or possible due to costs, preventive vaccine or passive antibody interventions may be cost-effective.

Passive immunity studies with HIV-intravenous immunoglobulin (HIVIG) in mother-infant pairs in the United States (ACTG 185) and in Uganda are under way. Studies in Haiti also are planned for immunoprophylaxis in infants who are breastfed by their HIV-positive mothers. Studies with monoclonal antibodies or related products are under consideration. With the success of AZT therapy, passive immunity approaches should be considered only as adjuncts to antiretroviral therapy in developed countries.

Additionally, the parallels between perinatal HIV and hepatitis B virus (HBV) transmission encourages investigations of active vaccine plus passive immunity approaches. Active immunization with hepatitis B vaccine begun at birth, with or without passive immunization with hepatitis B immune globulin (HBIG), is highly effective in preventing perinatal HBV infection and the development of chronic HBV infection. A logical extension of current studies of HIVIG to protect infants born to HIV-infected women would be vaccine trials in the infants, also with or without HIV immune globulin. Failure of HIVIG to protect infants should not deter undertaking vaccine approaches. Passive immunoprophylaxis had little effect in preventing HBV infection (although it clearly delayed the onset of infection and reduced the chronic carrier rate) whereas active induction of immunity by vaccine alone or vaccine with HBIG was highly effective. Thus, trials of HIV vaccines in high-risk newborns should be considered if populations and appropriate vaccines are available.

Several Phase I studies on HIV-1 envelope candidate vaccines in HIV-infected pregnant women or in infants born to HIV-infected mothers are either nearing completion or continuing followup. These pediatric or maternal transmission clinical trials with HIV vaccines have been conducted through collaborations between the AVEG and the Pediatric ACTG. A Pediatric Vaccine Working Group with representatives from AVEG and ACTG have collaborated on these activities. These trials were not coded in the vaccine area by either NIAID or by NICHD.

Infants born to women in HIV vaccine clinical trials provide a unique opportunity to study mechanisms of infection and protection, and if adequate samples are available, may be the optimal way to answer critical questions about transmission and acquisition of disease. Recent anecdotal observations that, in rare cases, infants may clear HIV infection could provide a remarkable tool to examine the protective immune responses to HIV, if additional such infants are identified. Because data on reduction of viral load do not appear to explain the reduction in transmission observed, surveillance of AZT-treated women and their infants should be increased to identify possible rare transient virus infections for detailed immunology studies.

As with vaccines for adult populations, the basic research underpinning the clinical trials effort for either active or passive immunity in children is meager. As part of long-term vaccine goals, studies in infant primates with vaccine vectors or candidate vaccines specifically designed for childhood vaccines should be initiated as soon as constructs are available. This is essential because the strategy that would be most effective in preventing transmission of HIV as well as other STDs in young adults (now recommended for Hepatitis B) would be vaccination in childhood with subsequent boosting in preteen, school-age children. This would ensure that strong recall priming of memory T cells would be possible and might permit the incorporation of an AIDS vaccine in a standard childhood vaccine regimen.

IV. Appendixes on Special Issues

Appendix 1. Links to Other Panel Reports

A number of programmatic components and general issues that concerned the Panel are also discussed in reviews performed by the other Area Review Panels. These cross-cutting issues are identified here (please see the reports of the other Area Review Panels for their independent assessments).

Identification of HIV Vaccine and AIDS-Related Activities

As noted in the body of the report, the Panel had considerable difficulties in accurately determining how much actual vaccine-related research was being performed in different vaccine research programs and distinguishing between vaccine-related and other categories of HIV/AIDS research. These difficulties were complicated by the current system of coding, which is not easily aligned with programmatic areas. In some instances, projects or budgetary items appeared to be assigned arbitrarily to the different AIDS coding categories; in others, misclassification of resources was systematic. Two areas of particular concern to this Panel were (1) the systematic failure to code many of the HIV/AIDS or AIDS-related immunology projects on correlates of immune protection to the Basic Vaccine Research category and (2) the coding, by both NIAID and FIC, of a substantial block of epidemiology and prevention projects as Infrastructure/Vaccine Clinical Trials. Other Area Review Panels identified similar problems, indicating that it is necessary to institute a major overhaul of the coding system used to track the allocation of resources allocated within the HIV/AIDS research budget.

As the coding system and information provided by the ICDs to the Panel was sometimes confusing and imprecise, OAR is urged to undertake an in-depth assessment of this problem to accurately identify the use of AIDS-related funds.

Reprogramming of Resources

The Panel uncovered a small but significant pool of resources that were allocated to projects coded as HIV vaccine-related research but whose title and abstract bore little or no apparent connection to HIV/AIDS research. This was largely a problem in the NCI intramural program at FCRDC, in the FIC Fellowship and small grants projects, and in the high levels of AIDS funds allocated to nonhuman primate research by NCRR. Such monies should be reprogrammed to bona fide HIV vaccine research activities.

Peer Review

The Panel concluded that one of its major concerns about the current peer review system was the lack of synchrony with the mission or goals for the HIV/AIDS vaccine programs defined in the NIH Plan for HIV-Related Research. Otherwise stated, there is a major disconnect between programmatic goals and the current review process. Consequently, many worthwhile research

activities that could provide essential knowledge for vaccine development are not appreciated by review groups that are either unaware of programmatic needs or are not experts in the vaccine area and do not recognize the critical but somewhat pragmatic nature of translational research. The Panel calls for the establishment of a special review group for the vaccine area as one of its major recommendations and appreciates that this is a problem shared by other thematic areas.

NCRR

No formal review of NCRR-sponsored HIV/AIDS vaccine-related activities was undertaken. However, Panel members identified several concerns about how AIDS resources were allocated and used within Regional Primate Research Centers (RPRCs). The problem of developing vaccines in the SIV macaque model has been hampered by the use of experimental groups with only a few animals in each and the inability to do comparative studies with different virus challenges. Both of these problems stem from the lack of sufficient nonhuman primate resources, either at the RPRCs at other sites performing AIDS vaccine studies. Furthermore, there are serious concerns that there may not be adequate resources in the Centers to provide sufficient housing for the numbers of animals infected with AIDS viruses. The need for long-term housing of experimental nonhuman primates has greatly increased because vaccinated animals, protected from disease and not simply from virus infection, may need to be studied over long periods of time for viral load assessments and other measures of vaccine efficacy. Related problems were identified by other Panels.

Recommendations

- **OAR and NCRR should make AIDS resources available through open, competitive review to investigators who seek to perform "pilot" vaccine studies. NCRR should devise a system to ensure access to animals for AIDS vaccine studies by non-RPRC investigators.**

- **NCRR should work with OAR and research teams studying AIDS vaccine approaches to provide adequate animal resources for testing novel vaccines, both at the RPRCs as well as at other sites.**

- **NCRR should better coordinate and integrate its HIV/AIDS vaccine research activities with other ICDs to allow better planning for nonhuman primate research resources.**

These recommendations should be considered in tandem with parallel reviews of NCRR by the Drug Discovery and Etiology and Pathogenesis Review Panels.

NCI

The Panel's review of NCI's HIV vaccine-related activities revealed an atypical distribution of resources relative to other ICDs. There appeared to be an excessive emphasis on intramural research in the HIV/AIDS vaccine area. In addition, there was also a large proportion of the funds associated with contracts to further support these and other intramural activities. Other ARP reviews reached similar conclusions. The NCI vaccine effort is poorly coordinated within the Institute and with other NIH vaccine-related activities. The Panel urges that the NCI activities in HIV vaccine research be carefully evaluated, streamlined, centrally coordinated and closely linked, wherever possible, to other ICD efforts.

The HIVNET Program of NIAID

The HIVNET program was reviewed by this Panel as well as by the Natural History, Epidemiology, and Prevention Panel and the Behavioral, Social Science, and Prevention Panel. Although the vaccine preparedness activities are amply covered by the Vaccine Panel, other activities of HIVNET that include behavioral and biomedical interventions as well as the potential epidemiological value of its initial study cohorts are best addressed in the reports of these other Panels. Collectively, these Panels have called for a reassessment of HIVNET by an expert panel to address issues of how to best maintain this valuable network for future vaccine and prevention research studies.[*]

[*] NIAID has responded to the NIH AIDS Research Program Evaluation Working Group Report and has constituted, with OAR input and approval, an ad hoc review panel to review the several complex and interrelated areas of research and the agenda proposed by the HIVNET investigators.

Appendix 2. Coding of HIV Vaccine Resources

Expenditures on HIV/AIDS vaccines in FY 1994 was reported at about $113 million according to the present ARIS database and the current coding system for projects as applied by various ICDs. The Vaccine Research and Development Area Review Panel examined the extramural and intramural components of NIH vaccine-related activities and concluded the following:

1. The present coding system presents significant difficulties in accurately assessing the level of resources within the areas defined by the NIH Plan for HIV-Related Research (e.g., vaccines versus pathogenesis, behavioral, or epidemiologic research). It appears that a substantial proportion (up to 20 percent) of the research coded as HIV/AIDS vaccines actually should be coded in other areas of AIDS or non-AIDS research.

2. Misclassification of non-AIDS research expenditures in AIDS or AIDS-related categories has occurred in some ICDs.

3. It was difficult to assess the level of funds expended for specific areas of the NIH Plan because some contract research, reagent repositories, and administrative support activities cannot be divided easily by either scientific project or NIH Plan areas. If the support activities cover several different areas, the amounts specified can change from year to year.

Thus, often it was not possible to accurately determine whether the allocation and expenditure of resources for HIV/AIDS vaccine research and development was appropriate. The assessment that follows can therefore only be considered a "best effort" estimate that outlines the current situation and provides a starting point for a more precise definition of the scope of the NIH vaccine programs.

Of the nearly $113 million coded as HIV/AIDS vaccine research, approximately $89 million appears to have been appropriately designated. The remaining projects represent (1) research that may have been designated appropriately as AIDS or AIDS-related research that is only tangentially related, at best, to vaccine efforts (about $18 million) and (2) research that does not appear to be AIDS-related (about $6 million). Overall, this analysis suggests that considerably fewer dollars were actually spent on bona fide HIV/AIDS vaccine research than has been reported for FY 1994.[*]

[*] During the process of review and writing this report, several of the ICDs, namely NIAID, NCI, and FIC, addressed some issues of coding that were identified by this Panel. NIAID coded the HIVNET project in FY 1995 to more adequately reflect the epidemiological and natural history AIDS research being conducted in those cohorts. The NCI administration has begun an extensive revision of its intramural budgeting and coding process.

Some examples of the projects totalling $18 million that were appropriately identified as AIDS-related but which were probably inappropriately coded as vaccine-related research are:

1. Intramural research at NIAID that would be more appropriately coded as AIDS pathogenesis research ($2.1 million).

2. All costs of chimpanzee and specific pathogen free (SPF) macaque breeding funded through NCRR ($4.1 million and $2.1 million respectively). These funds are independent of any research funds spent on experimental vaccine studies.

3. Many aspects of the FIC training programs in epidemiology (in particular the AITRP; $6.8 million coded to the vaccine clinical trials infrastructure category, 4B) are more clearly epidemiology than vaccine-related. (This is fully discussed in the Clinical Vaccine Trials Subpanel section of this review.)

4. Support mechanisms for reagents, shared resources, and services that extend beyond vaccines. This was a particular problem for a series of four large-budget allocations (totalling $6.3 million) identified by NCI only as "Operations and Technical Support" for FCRDC. This allocation was in addition to a budget item ($2.98 million) identified as "Evaluating Lentivirus Compounds as Vaccines in Animals," which was described as monies transferred to DoD for "overhead" at the FCRDC facility. These allocations were not clearly associated with any projects, but it was estimated that at least $3 million could not be justified in the basic vaccine research category.

It also was determined that some bona fide vaccine-related research had been coded to topics in Etiology and Pathogenesis and, to a lesser extent, as Epidemiology or Prevention research. Thus, some fraction of each of those categories also appropriately might be reclassified.

> For example, essentially all of the grants on cellular immunology and CTLs, even those investigating T-cell epitopes. have been assigned to an Etiology and Pathogenesis budget code, 2A, whereas many of the grants on humoral immunity have been assigned to basic vaccine research category, 4A. Both of these areas fit logically into basic research for the design of vaccines to induce protective immune responses. Another example is the Correlates of HIV Immune Protection Contract, which was coded as category 2A rather than 4A, although one of the stated goals of that contract was to evaluate the immune responses of vaccinees who failed to be protected by candidate vaccines. Furthermore, research on vaccinees as well as basic research on correlates of immunity relevant to vaccine design has been conducted under that contract. At the same time, an interagency agreement for the statistical analysis of studies performed on the contract is appropriately coded 4C. Both projects are administered through the DAIDS.[*]

[*]The Correlates of HIV Immune Protection Contract is now scheduled for termination in June 1997. NIAID intends to shift the $3 million currently allocated for this contract to investigator-initiated, peer-reviewed grants. The need for other research and development contracts in the vaccine areas will be reviewed by NIAID with the OAR if they are proposed for renewed funding.

The Panel identified a number of projects that were clearly non-AIDS activities misclassified as HIV vaccine-related research including the following:

a. About $1.5 million was coded for one component of NCRR's GCRC awards (M01). This appeared to duplicate funding for AIDS projects that were funded by an NIAID-sponsored AVEG contract and represented about half of the total budget allocated to AIDS vaccine clinical trials research by NCRR.

b. Intramural research at the NCI (Z01) relating to peptide vaccines against cancer viruses and oncogenes ($257,000) was coded as AIDS vaccine research. NCI research on HIV peptides is funded appropriately under this same project.

c. Several projects supported through the FIC small grants programs had titles and abstracts that were related to infectious diseases in developing countries but had little direct relevance to AIDS research.

d. An excessive amount specified for "Operations and Technical Support" for intramural research at NCI, FCRDC was coded as HIV/AIDS vaccine research. A precise estimate of the miscoding is difficult, but the sum is likely to be in excess of $3 million (about half of the budget for this item) in this category.

These issues notwithstanding, Table 2 presents a rough approximation of the resources according to the vaccine categories evaluated by this Panel—Basic Research, Targeted Research, and Clinical Trial Research. Clearly evident from this breakdown is the paucity of resources for support of extramural research in both the Basic ($12,428,823) and Targeted ($17,122,643) research categories, compared with funds for Clinical Trials networks ($32,943,191). With the exception of Clinical Trials Research, intramural research received roughly one-third of the total funding in these areas, despite a great disparity in the number of investigators being supported: many more extramural investigators (45 research project grants) than intramural investigators (14 Z01 projects).

In view of these and other considerations expressed in this report, the first priority for additional or reprogrammed funds should be to increase the level of extramural investigator-initiated research.

Table 2. NIH HIV-Related Vaccine Research FY 1994

	Basic Research	Targeted Research	Clinical Trials Research	Other	Total
Extramural	$12,428,823 (a)	$17,122,643 (b)	$32,943,191 (c)		$62,494,657
Intramural	6,626,524 (d)	8,768,728 (d)	[000] (e)		15,395,252
Primate Resources		14,519,676 (f)			14,519,676
General Infrastructure (g)			8,334,446 (g)		8,334,446
Administration (h)	1,649,548	1,900,300	3,659,895	4,955,988	12,165,731
TOTAL	**$20,704,895**	**$42,311,347**	**$44,937,532**	**$4,955,988**	**$112,909,762**

a. Extramural Basic Research includes all unsolicited, investigator-initiated grants (R01, R29, R03, R37, R43, R44; Physician-scientist and fellowship awards K08, K11, F05, F06 and components of a P01 coded HIV vaccine research).
b. Targeted Extramural Research includes grants and contracts solicited through RFAs and RFPs; CMIG R01s, NCVDG and Adjuvant cooperative agreements (U01s), R & D contracts on genetic variation, and related smaller efforts.
c. Extramural Clinical Trials Research consists of the AVEG and HIVNET efforts, including all of the associated laboratory and statistical center contracts. Amounts for FY 1994 are artificially high for 2 reasons: First, the timing of expenditures for the HIVNET and AVEG resulted in 15 to 18 months of funds being allocated in a single fiscal year. Second, both NIAID and FIC coded substantial amounts of their AIDS budget to the development of Infrastructure for Vaccine Efficacy Trials, when some of these projects or activities might have been more appropriately coded as natural history and epidemiology research.
d. Intramural HIV/AIDS vaccine research, conducted at NCI and NIAID (coded 4A) was divided by project content. Several projects similar to NCVDG awards with accompanying primate resources were included in the Targeted Research.
e. Intramural HIV/AIDS vaccine clinical trials have been conducted by NIAID and NCI in the past, and are ongoing in FY 1996; no funds were identified for this activity in FY 1994.
f. Primate Resources included are: RPRCs, $2.5 million; SVEUs $3.1 million; Contracts for primate resources for intramural investigators, $2.3 million; SPF macaque breeding, $2.1 million; and chimpanzee breeding, $4.1 million. RPRCs funds also support some Basic Research on vaccines as do resources for some of the cooperative agreements and other investigator-initiated, solicited projects included in the targeted research.
g. General Infrastructure represents the GCRC support, $2.56 million; and FIC (training programs: D43 awards $5 million, and T22 awards, $0.77 million). The coding of GCRC activities at one Center by NCRR resulted in an inflated amount of funds attributed to vaccine research at clinical centers.
h. Administration included research management support (RMS), which covers staff salaries, services, program reviews, conferences, meetings, etc., intramural support (FCRDC) contracts that did not appear to fit a single category.

Appendix 3. NCRR-Supported Nonhuman Primate Resources

Two factors initiated the early disease model development and AIDS vaccine experimentation in nonhuman primates. The first was the identification of several SIV isolates that induced AIDS in rhesus or pigtailed macaques at four of the Regional Primate Research Centers (RPRCs). The second was the discovery that some early isolates of HIV could infect chimpanzees, a species that had proven extremely valuable for the development of vaccines against hepatitis virus.

A major component of nonhuman primate resources dedicated to AIDS research are the RPRCs. These Centers, administered by NCRR, were established 30 to 35 years ago so that the biomedical research community could benefit from regional facilities with expertise in research with nonhuman primates. There are seven RPRCs in the country: California, Georgia (Yerkes), Louisiana, Massachusetts, Oregon, Washington, and Wisconsin. While each is a distinct organization affiliated with a major academic institution, each receives operating support from NIH.

RPRC	Location	Host Institution
New England	Southborough, MA	Harvard Medical School
California	Davis, CA	University of California, Davis
Washington	Seattle, WA	University of Washington
Oregon	Portland, OR	Oregon Health Sciences Center
Wisconsin	Madison, WI	University of Wisconsin
Yerkes	Atlanta, GA	Emory University
Tulane University (Delta)	Covington, LA	Tulane University

Recent program guidelines issued by NCRR for the RPRCs state that the overall objective of the program is to provide specialized resources (physical facilities, technology, professional and technical staffing, and a variety of primate species) for research studies applicable to the solution of human health problems. Of importance for this review on AIDS vaccine-related research, it is noted that RPRC funds should be utilized to:

1. Conduct meritorious basic and applied biomedical research in areas requiring the use of primates.

2. Develop improved practices of primate breeding, husbandry, and genetic definition to help meet research needs for pedigreed, disease-free animals of defined quality, and to assure the continued availability of species of biomedical research importance whose wild populations are considered threatened or endangered.

3. Provide opportunities for research development and experience in primatology to trainees at various levels of experience.

4. Provide regional and national resources to support primate-related research, including data collection and management, consultative expertise, biologic and genetic material, and specialized facilities and equipment.

Each RPRC receives operating base grant support from NCRR. Base grant funds awarded by NCRR provide support for infrastructure and resource-related expenses as well as a portion of each Center's programs in AIDS and non-AIDS research. Other disease-specific research activities at RPRCs, including AIDS research, are also supported by NIH grants from other ICDs and from other sources including pharmaceutical firms and non-Government research funding groups. Base grant support from NCRR accounts for approximately 40 to 60 percent of the research and operating costs of each of the RPRCs. AIDS research supplements were initially awarded to the individual Centers based on their capability of pursuing specific AIDS-related research activities. These AIDS "supplements" were subsequently incorporated into RPRC Base Grant renewals and this development has resulted in some of the concerns that have been raised by the Panel in its review of this portfolio of grants.

The RPRC program has contributed substantially to the overall AIDS effort since AIDS-targeted support was initiated in 1984. The RPRC Base Grants funded the following: the original identification and isolation of SIV and its association with an AIDS-like disease; reproduction of AIDS like-disease in readily available laboratory primates with both cloned and uncloned SIV; development and testing of vaccine concepts; evaluation of the relative effectiveness of different vaccine concepts; and investigation of fundamental mechanisms of viral pathogenesis. Reliance on primate models to better understand pathogenesis and immune-mediated control of AIDS viruses has been made possible principally through this previous long-term commitment to high-quality primate resources. While far from ideal, the RPRC program has clearly made critical contributions to the nation's AIDS research effort and to the HIV/AIDS vaccine efforts in particular.

In addition, funds coded solely to the AIDS vaccine effort have been allocated by NCRR for specific pathogen-free (SPF) macaques. The scientific need and the extent to which these resources are used for AIDS research, and specifically the HIV/AIDS vaccine effort, should be reviewed carefully. It was noted that SPF macaques were recently utilized in experiments to address critical co-infection issues with attenuated virus vaccine concepts. AIDS pathogenesis questions may require further use of these animals, and some budget allocation might be more appropriately coded as AIDS pathogenesis.

In response to concerns previously raised about the research conducted at RPRCs and about access to nonhuman primate resources, the RPRCs have recently increased efforts to include scientists not affiliated with the RPRC and to institute local systems for external evaluation of meritorious proposals. Some RPRCs have been responsive to investigators seeking access to experimental resources for small "test of concept" types of vaccine experiments. Part of the constraint is the limited availability of resources, particularly holding space for lentivirus-infected animals, beyond those previously committed to funded studies by primate center

investigators. Finite resources at the RPRCs do not allow for expansion. It is not always appreciated that independent support for research activities at the RPRCs is usually required, even for investigators at the RPRCs. Furthermore, in some cases investigators at the RPRCs are forced by limitations at the Centers to conduct a large part of their investigations on contract with private firms outside of the RPRCs. Nevertheless, if the pool of resources to support animal research at RPRCs is increased and opened to competition (see below), this configuration could change to permit the rapid inclusion of additional novel meritorious research. To achieve this goal, the Panel recommends that a system for evaluating AIDS-related proposals on a national basis through NIH (DRG) study sections rather than by the individual RPRC would be more equitable. It also should be possible to reserve a portion of each Center's AIDS-related resources strictly for access by investigators not affiliated with the Center. To ensure the appropriate use of these valuable nonhuman primate models, new non-RPRC investigators proposing studies could work with RPRC investigators on study design issues. To maximize the quality of research, the Panel recommends that NCRR (or DRG) institute ongoing review mechanisms, including experts in other areas of AIDS research, to ensure that AIDS research programs at RPRCs are stringently evaluated and that funds are awarded in a competitive fashion. Simultaneous peer review of AIDS-targeted Base Grant support to all of the seven RPRCs should also be considered, in contrast to the nonconcurrent, cyclical review of this research which is now linked to general review of the individual Center.

The Panel commends RPRCs that have successfully recruited high-caliber staff in immunology and virology and built interactive teams to perform research on AIDS vaccines. The Panel wants to ensure that such programs are not dismantled because of a failure to recognize the importance of translational research, particularly in immunology. Guidelines should be formulated for the award of AIDS research funds from NCRR such that stronger interdisciplinary AIDS research programs are formed and appropriately funded.

In the Panel deliberations, questions were raised about the extent of AIDS-related primate research that is conducted at nonhuman primate facilities not associated with the RPRCs, and about how this is funded and linked with research that is conducted at RPRCs. It is readily acknowledged that the RPRCs do not have the capacity or the flexibility to accommodate all of the AIDS-related research that would be optimal for AIDS vaccine research and development. However, funding of nonhuman primate research at diverse sites should be incorporated as part of the complete NIH Plan for HIV-Related Research to ensure that small primate facilities with valuable resources and only one or two investigators are kept informed of rapidly moving research goals.

As a result of strong NIH support for investigator-initiated studies in the United States, a broad array of pathogenic SIV, HIV-2, and SHIV isolates for analysis of pathogenesis and vaccine-related issues have been developed. This diversity can be viewed as a healthy exploration of isolates with different pathogenic potential, comparable to the range of isolates that exist in human HIV-1 disease. However, one inherent problem of investigator-initiated research with primate models in the vaccine research area is the difficulty in comparing results from different laboratories using different animal models to evaluate vaccine approaches. For example, it is difficult to compare the results of one laboratory using virus A, neutralization assay B, and virus quantitation assay C with the results of a second laboratory using virus X, neutralization assay

Y, and virus quantitation assay Z. This has been a problem in the United States for at least 6 years. The comparison of different models might be resolved by cross-comparison of end points with new forms of measurement such as viral load. A plan for systematic, comparative evaluation of vaccine approaches and associated variables is still desirable. Large comparative studies in monkeys can be achieved either through a centralized testing facility (the approach taken by the Medical Research Council in England) or through team-organized simian vaccine evaluation studies (the approach of the AIDS vaccine study group supported by the European Economic Community). A third approach has been instituted by NIAID for experimental design approval by a group of extramural, non-Government research scientists and Program Staff for utilization of contract-supported nonhuman primate resources for studies, some of which are conducted at RPRC sites. Coordinated support through NCRR and NIAID, and other relevant ICDs, should be developed for well-designed comparative AIDS vaccine activities.

Finally, OAR should facilitate the reevaluation of the issue of AIDS-related chimpanzee resources with two objectives in mind. One objective is to determine whether the cost being borne by the NIH AIDS research budget (about $4.1 million) for chimpanzees is appropriate. These costs are independent of costs for use of the animals in vaccine experiments because most of the chimpanzees are now at breeding facilities where AIDS research cannot be conducted because biohazard containment facilities are not available. The second objective is to determine how to support testing and availability of HIV stocks for chimpanzees and the type of viral stocks that are needed for critical vaccine evaluation. Because the National Research Council is evaluating the broader issue of the use of chimpanzees in biomedical research and their long-term care, the OAR, through the NIH AIDS Vaccine Coordinating Committee, should consider findings from that review in its evaluation.

Appendix 4. Target Areas for Application of Additional Resources in HIV/AIDS Vaccine Research

A principal recommendation of the Vaccine Research and Development Area Review Panel is that NIH should expand the scope and dimensions of the HIV/AIDS vaccine program. One of the highest priorities is to increase funding for basic research as defined by the Basic Research Subpanel. These funds should encourage and support research on human and nonhuman primate systemic and mucosal immunology, and on novel concepts in design of immunogens and delivery systems. Investigation is needed to understand the early events in natural HIV infection that limit the HIV replication level in some individuals. As the Panel noted previously, such funds must be applied in concert with establishment of a supportive "culture" for both basic and pragmatic aspects of all vaccine research to yield success for this endeavor.

Appreciable funds also will be necessary to support the preclinical evaluation of vaccines in animal models, with derivation of immune correlates as described in the Targeted Vaccine Research Subpanel report. Although such funds are not of higher priority than those for Basic Research, they can be applied more rapidly, as determined by the NIAID Vaccine Design Focus Group guiding this area. Nevertheless, a careful assessment must be undertaken promptly to determine the needs for comparative vaccine testing relative to the needs for evaluation of novel vaccine concepts worthy of testing.

The area described as Clinical Trials Research, which includes AVEG and HIVNET, does not appear to have an immediate need for additional funds for vaccine research. The Panel recommends that NIAID review the HIVNET program and use its review to make the best use of the cohorts and funds currently available. This may require that some funds be redirected to other areas of AIDS vaccine research. At the present time, it is unlikely that an efficacy trial could begin before 1998. If the overall HIV/AIDS vaccine program is expanded and becomes invigorated as recommended by this review, the vaccine pipeline should be filled with promising HIV candidate vaccines, making it likely that additional resources will be required in the near future for both the AVEG and HIVNET.

Appendixes
Supporting Materials

A. Schedule of Meetings/Conference Calls and Deadlines for the Panel

January 29, 1995	Evaluation Working Group and Area Review Panels (ARP), Chairs meeting, Washington, D.C.
May 3	Vaccine Research and Development Area Review Panel (Vaccine ARP) meeting; Gaithersburg Hilton, Gaithersburg, MD.
May 5	Vaccine ARP Conference call with members not able to attend May 3 meeting, 2:00 pm EDT.
May 18	Vaccine ARP Clinical Evaluation Trials Subpanel teleconference, 4:00 pm EDT.
May 31	Vaccine ARP Clinical Evaluation Trials Subpanel teleconference, 4:00 pm EDT.
June 7	Vaccine ARP teleconference, 1:00 pm EDT.
June 16	Executive Secretaries meeting with Dr. Marvin Kalt, NCI.
June 20	Targeted Vaccine Subpanel, teleconference at 1:00 pm EDT.
July 10	Evaluation Working Group and ARP Chairs meeting, Bethesda, MD.
July 10-11	Vaccine ARP meeting, Bethesda, MD. Presentations by ICD Program Staff and representatives of selected non-NIH vaccine programs.
July 20	Teleconference with Drs. Levine and Paul with ARP Chairs, 11:00 am EDT.
August 10-11	Evaluation Working Group and ARP Chairs meeting, Bethesda, MD
August 24	Vaccine ARP Clinical Trials Subpanel conference call, 11:00 am, EDT.
August 30	Vaccine ARP meeting, NIH, Bethesda, MD. Discussion of rough drafts of vaccine subpanel and topic reports; identification of issues for further investigation.
September 13	Evaluation Working Group and ARP Chairs meeting, Bethesda, MD. (Public Session)
October 2	Joint ARP conference call with NIAID staff about HIVNET, 3:00 pm EDT.
October 12-13	Evaluation Working Group and ARP Chairs meeting, Bethesda, MD. (First draft of Executive Summary reviewed by Vaccine Panel Members.)

October 16	Vaccine Research and Development ARP meeting, Crystal City, VA (Public session).
December 14-15	Evaluation Working Group and ARP chairs meeting, Hyatt, Bethesda, MD. (First complete draft of Subpanel reports. Sent December 23 to all Panel members.)
February 6, 1996	Revised draft of Vaccine ARP Subpanel reports distributed to Panel for comment.
February 15-16	Evaluation Working Group and ARP Chairs meeting, Bethesda, MD.
February 26-27	Evaluation Working Group and ARP Chairs meeting, Bethesda, MD.
March 6	Completed draft report distributed to Evaluation Working Group, Office of AIDS Research Advisory Council (OARAC), and ICD Directors.
June 13-18	Final draft report, with revised appendices, sent to Panel members.
June 25	Final report sent to Evaluation Working Group, and OARAC for approval. Copies provided to ICD Directors.

Note: This list does not contain several Subpanel teleconferences at which fewer than 4 members addressed subtopic issues.

B. Invited Presentations

The Vaccine Research and Development Area Review Panel would like to particularly thank the people listed below who, through interviews, presentations, or conversations and the submission of written materials, provided information important for Panel deliberations.

NIH Staff Presenting Information at Vaccine Area Review Panel Meetings:

Inese Beitins, M.D.
Associate Director for Clinical Research
NCRR
Bethesda, MD

Raoul Benveniste, M.D.
Medical Officer
Laboratory of Viral Carcinogenesis
FCRDC, NCI
Frederick, MD

Jay Berzofsky, M.D.
Chief, Molecular Immunogenetics and Vaccine Research Section, NCI
Bethesda, MD

Lawrence Deyton, M.D.
Chief, HIV Research Branch,
DAIDS, NIAID
Bethesda, MD

Richard Dukelow (no longer with NIH)
Comparative Medicine Branch
NCRR
Bethesda, MD

Patricia Fast, M.D., Ph.D.
Associate Director, Vaccine and Prevention Research Program
DAIDS, NIAID
Bethesda, MD

Rodney Hoff, D.Sc., M.P.H.
Chief, Efficacy Trials Branch
DAIDS, NIAID
Bethesda, MD

James McNamara, M.D., Ph.D.
Chief, Vaccine Trials Branch
(Pediatric Medicine Branch)
DAIDS, NIAID
Bethesda, MD

Peter L. Nara, D.V.M., Ph.D.
Chief Virus Biology Section
Laboratory of Tumor Cell Biology
NCI, FCRDC
Frederick, MD

Malcolm Martin, M.D.
Chief, Laboratory of Molecular Microbiology
NIAID
Bethesda, MD

Jerry Rice, Ph.D.
Chief, Laboratory of Comparative Carcinogenesis
NCI, FCRDC
Frederick, MD

Margaret (Peggy) Johnston, Ph.D. (no longer with NIH)
Deputy Director
DAIDS, NIAID
Bethesda, MD

Marjorie Robert-Guroff, Ph.D.
Chief, Immune Biology of Retroviral Infection
Research Section
NCI
Bethesda, MD

Alan Shultz, Ph.D.
Chief, Preclinical Research Branch
DAIDS, NIAID
Bethesda, MD

Bernard Talbot, M.D., Ph.D.
Medical Officer, Clinical Research
NCRR
Bethesda, MD

We also wish to thank the many other staff at NIH who assisted our efforts throughout the year, providing information and handling queries; in particular Sharilyn Stanley, M.D., NIAID; Kenneth Bridbord, M.D., FIC; Judy Karp, M.D. and Alan Rabson, M.D., NCI; and Larry Arthur, Ph.D., NCI, FCRDC.

Presenters from Non-NIH Organizations:

Seth Berkeley, M.D.
Rockefeller Foundation,
International AIDS Vaccine Initiative

Deborah Birx, M.D.
Walter Reed Army Institute for Research

John McNeil, M.D.
Walter Reed Army Institute for Research

Michael Wyand, D.V.M.
TSI Mason Laboratories

Presentations or Written Testimony Provided to the Panel at the Public Meeting October 16, 1995

Ronald Moss, M.D.
Medical Director
Immune Response Corporation
Carlsbad, CA 92008

Dr. Junko Otani
AIDS Specialist
The World Bank, ASTHR
Washington, D.C. 20433

Sharon Frey, M.D.
Assistant Professor
Saint Louis University
St. Louis, MO 63110

George Woody, M.D.
Chief, Substance Abuse Treatment Unit
VA Medical Center
Philadelphia, PA 19104

Bryan E. Roberts, Ph.D.
Virus Research Institute
Cambridge, MA 02139

Wayne Koff, Ph.D.
Vice President, Vaccine Research & Development
United Biomedical, Inc.
Hauppauge, N.Y. 11788

Donald Francis, M.D. D.Sc.
Clinical Scientist
Genentech, Inc.
San Francisco, CA 94080

Jim Thomas
National Community Advisory Board
St. Louis University
St. Louis, MO 63110

Edward S. Neiss, M.D.
Medical Director
Albert Sabin Vaccine Foundation
New Canaan, CT 06840

C. Biographies of Panel Members

Abul K. Abbas, M.D., is Head, Immunology Research Division, Department of Pathology, Brigham and Women's Hospital, Boston, MA; Staff Pathologist, Brigham and Women's Hospital; and Professor of Pathology, Harvard Medical School, Boston, MA. He received his MBBS (MD equivalent) from All-India Institute of Medical Sciences, New Delhi, India. His research interests have been in cellular interactions in immune responses, cytokines, tolerance and autoimmunity, and structure-function analysis of B cell antigen receptors by mutagenesis. Dr. Abbas is the recipient of numerous awards and honors, has published extensively, and is a member of various editorial boards and professional societies and has served on NIH study sections in Immunology.

Dani Bolognesi, Ph.D., is Director of the Center for AIDS Research at Duke University Medical Center and Co-Director of the Human Vaccine Institute. He leads an active research program in HIV biology, vaccines, and immune reconstitution. Dr. Bolognesi has participated in numerous advisory committees in the vaccine area such as the AIDS Vaccine Selection Group, the AIDS Vaccine Working Group, and the WHO Vaccine Steering Committee. His laboratory group also serves as the Central Immunology Laboratory for the AIDS Clinical Trials Vaccine Network. He has authored more than 200 publications in scientific journals, reviews, and textbooks and is the Editor-in-Chief of *AIDS Research and Human Retroviruses*.

Lawrence Corey, M.D., is Professor, Departments of Laboratory Medicine and Microbiology, Adjunct Professor, Departments of Medicine and Pediatrics, University of Washington, Seattle, WA. He received an M.D. from the University of Michigan Medical School, Ann Arbor, MI. Dr. Corey's interests have focused on therapy against infectious diseases, especially STDs. He was a leader in the early development of the ACTG and served as the chair of the Executive Committee. He has also served as chair of the AVEG Executive Committee and a member of the NIAID Vaccine Working Group. Dr. Corey has published nine books, over 200 articles, and numerous chapters and editorials. He is a member of many national international academic and grant research committees, as well as editorial boards, in particular *Journal of Infectious Diseases*.

Ronald C. Desrosiers, Ph.D., is Professor of Microbiology and Molecular Genetics at Harvard Medical School, Chairman of the Microbiology Division at the New England Regional Primate Research Center (NERPRC), and Coordinator of the AIDS Unit, NERPRC. He received a Ph.D. from Michigan State University, Department of Biochemistry, and an honorary M.S. from Harvard University. Dr. Desrosiers has served on a number of university, industrial, and Government advisory panels, on grant review committees including the DRG ARRA study section, and on the editorial boards of several journals. He has published extensively in peer-reviewed articles, reviews, and book chapters. He has been at the forefront of the development and use of simian immunodeficiency virus (SIV) models for HIV infection, including the analysis of pathogenesis of molecularly attenuated forms of SIV and their use for AIDS vaccine development.

Ellen Heber-Katz, Ph.D., is Professor of Pathology and Laboratory Medicine and Professor of Neurology, University of Pennsylvania School of Medicine, Philadelphia, PA. ,She received a Ph.D. from the University of Pennsylvania in 1976. Dr. Heber-Katz did postdoctoral training at the Laboratory of Immunology, NIAID, NIH, Bethesda, MD, and has been at the Wistar Institute since 1982. Her main interests are the T-cell response to self and nonself antigens, T-cell receptors, autoimmunity and its regulation, and antiviral immunity. Dr. Heber-Katz has been a member of many ad hoc and research review committees, served on

editorial review boards of immunology journals, and published extensively on induction and regulation of T-cell immunity.

Maurice R. Hilleman, Ph.D., is Director, Merck Institute for Therapeutic Research, and Adjunct Professor of Pediatrics, School of Medicine, University of Pennsylvania, Philadelphia, PA. He received his B.S. degree from Montana State University in 1941 and a Ph.D. from the University of Chicago in 1944. Dr. Hilleman also holds several honorary doctorate degrees. He has been devoted to both basic and applied research and has been noted for many breakthrough discoveries and developments in virology, cancer, immunology, epidemiology, and vaccinology. He has achieved many accolades for the vaccines he developed and they are being used worldwide. From 1948 to 1958 Dr. Hilleman was Chief, Department of Respiratory Diseases, Walter Reed Army Institute of Research, Washington, DC. In 1951, he was a Visiting Investigator at the Hospital of the Rockefeller Institute for Medical Research. He received the Lasker Medical Research Award in 1983 and is an elected member of the U.S. National Academy of Sciences, the American Academy of Arts and Sciences, and the Institute of Medicine of the National Academy of Sciences. He was awarded the National Medal of Science by President Reagan. He was appointed by the Secretary of Health and Human Services to the National Vaccine Advisory Committee of the National Vaccine Program. More recent awards include the San Marino Prize for Medicine, given in 1989 by the Captains Regent of the Republic of San Marino; the 1989 Robert Koch Gold Medal for etiologic discovery and vaccine development, from the Robert Koch Foundation; and the Alumni Medal for Lifetime Accomplishment from the University of Chicago, given in 1987. He also received the Albert B. Sabin Medal given by the German Society for Social Pediatrics, and the Distinguished Scientist Award of the Southwest Foundation for Biomedical Research in 1988.
Dr. Hilleman has published over 460 original articles in the fields of virology, immunology, epidemiology, and infectious diseases. He serves on numerous national and international advisory boards and committees, academic, governmental, and private, and has been a member of the Expert Advisory Panel of the World Health Organization, Geneva, since 1952.

Bonnie J. Mathieson, Ph.D., is a Health Scientist Administrator and the Chair of the NIH Vaccine Research and Development Coordinating Committee at the Office of AIDS Research (OAR), Office of the Director (OD), NIH, Bethesda, Maryland. She received her B.S. at the University of Illinois,, did initial graduate studies in the Department of Medical Microbiology at Stanford, and received a Ph.D. at Cornell University Medical College, Sloan-Kettering Division of Graduate Studies, New York, NY. Dr. Mathieson trained as an immunologist and developmental biologist working on studies of T-cell surface marker expression, lineages of T-cells, differentiation of NK and CD8+ cells, and mechanisms of cytokine activity. She was awarded a postdoctoral training fellowship from the Cancer Research Institute, NY, and was a Staff Fellow in the Laboratory of Microbial Immunity, NIAID, NIH. From 1982-1983, she was a member of the Basel Institute for Immunology in Switzerland. In 1984, she joined the Cancer Institute (NCI) and became Head of the Leukocyte Differentiation Section, at NCI-FCRDC. In 1989, she joined the Division of AIDS (DAIDS), NIH, as a Project Officer in the Vaccine Research and Development Branch. For five and a half years, she monitored and encouraged research in the AIDS immunology and vaccine portfolios by reviewing progress reports, organizing workshops and meetings, and writing RFA and RFP proposals to support basic science related to vaccine design and delivery, particularly in areas of the immunology and virology of HIV. In July 1995, she joined the OAR to coordinate AIDS vaccine-related activities. Dr. Mathieson's awards include The Public Health Service Special Recognition in 1992 for her role in DAIDS Pediatric Initiative Group. She has published over 100 research articles and has served on editorial boards and ad hoc review groups and currently serves as a Councillor for the Clinical Immunology Society.

Jiri Mestecky, M.D., is a Professor in the Departments of Microbiology and Medicine, University of Alabama at Birmingham (UAB). He graduated from the School of Medicine, Charles University in Prague, Czechoslovakia 1964. Postdoctoral Studies were performed at the Czechoslovakia Academy of Sciences, Prague, in the Department of Immunology headed by Professor I. Sterzl, and at UAB with Professor I.W. Kraus. A sabbatical was spent in 1976 at Rockefeller University, New York, in the laboratory of Professor H.G. Kunkel. Dr. Mestecky is recognized as a leading authority in mucosal immunity and has developed systems for critical evaluation of samples from mucosal sites. He has served as a member of the editorial boards of the *Journal of Immunology*, *Immunochemistry* (Molecular Immunology), *Infection and Immunity*, *Journal of Clinical Immunology*, *Oral Microbiology*, *Immunology* and *International Archives of Allergy and Immunology*. He has authored over 300 papers, and chapters in 10 books.

John P. Moore, Ph.D., is a Staff Investigator at the Aaron Diamond AIDS Research Center and an Associate Professor at The Rockefeller University in New York City. He received his B.A., Masters, and Doctoral degrees from Cambridge University, UK. Dr. Moore has training as a Biochemist; his pre- and postdoctoral research focused on understanding the mechanism of T-cell stimulation by mitogens. Since 1987, he has been working in AIDS research with an emphasis on the structure, function, and immunogenicity of the HIV envelope glycoproteins. Before joining the faculty at the Aaron Diamond AIDS Research Center, Dr. Moore was a Post-Doctoral Research Scientist in the Department of Biochemistry, Cambridge, with short periods as Visiting Scientist in the laboratories of Dr. K. Kelly and Dr. M.A. Beaven, National Institutes of Health, Bethesda, MD; a year as Visiting Scientist in G.I. Evan's laboratory, Ludwig Institute for Cancer Research, Cambridge; and a year as Research Fellow at the Department of Veterinary Pathology, University of Glasgow. He also spent 3 years as Research Fellow of the Institute of Cancer Research with Dr. Robin Weiss, Chester Beatty Laboratories, London. Dr. Moore's awards include the Great Crosby Exhibition in Natural Sciences at Downing College, Cambridge, and election into a Bye-Fellowship at Downing College. He has published 100 research papers and has served on editorial boards and as a reviewer for numerous AIDS and virology journals. He has also served as an ad hoc member on several NIH study sections.

James I. Mullins, Ph.D., is a Professor, Departments of Microbiology and Medicine, and Adjunct Professor, Department of Laboratory Medicine, University of Washington School of Medicine, Seattle, WA. He received his Ph.D. in Cell Biology and Biochemistry from the University of Minnesota and did postdoctoral work at Harvard. Dr. Mullins has utilized molecular biology to study retrovirus pathogenesis for the last 18 years, including studies of FeLV, HIV, SIV, and FIV. He also has conducted basic research on retrovirus vaccines in all four systems for the past 9 years. He participated in the Genetic Variation Project of the WHO Global Programme on AIDS; developed test systems for identification of different genetic subtypes of HIV; and has participated in the ARIEL Research Project, sponsored by the Pediatric Aids Foundation. Dr. Mullins has published over 100 peer-reviewed articles and book chapters. He has been the recipient of numerous honors and awards and sits on many review committees and editorial boards.

Harriet Robinson, Ph.D., is a Professor of Pathology, University of Massachusetts Medical Center and Vice Chairman for Program in Immunology and Virology. She received her M.S. in Biochemistry and Ph.D. in Microbiology from the Massachusetts Institute of Technology. Prior to her arrival at the University of Massachusetts Medical Center in 1988, Dr. Robinson was a Principal Scientist at the Worcester Foundation for Experimental Biology; part-time Research Associate at Stanford University School of Medicine; and a National Science Foundation Postdoctoral Fellow in the laboratory of Dr. Harry Rubin. Her experience has been in retrovirology, and she is a pioneer in the development of a DNA vaccine. Dr. Robinson has published

extensively and served as a member of the NIAID AIDS Review Group. She participates in a number of professional and community activities and serves on several scientific boards.

William Snow, of ACT UP/Golden Gate, has advocated for AIDS vaccine development with active community involvement in the process since 1990. He has been instrumental in establishing national and local community advisory boards (CABs), for Phase I, II, and potential Phase III trials of candidate preventive vaccines at NIH. He has been a National CAB member for the AIDS Vaccine Evaluation Group and recently has been selected as a member of the HIVNET Governance Board. He has also actively followed trials of vaccines for therapy in HIV-infected persons and has been involved in ACTG efforts to study vaccines. He has participated extensively in the current OAR review and is helping to form a new national AIDS vaccine advocacy organization, A-VAC.

Kathelyn S. Steimer, Ph.D., is Vice President of Research of the Chiron Biocine Division of Chiron Corporation, a biotechnology company headquartered in Emeryville, CA. She received her Ph.D. in Microbiology in 1979 from the University of Pennsylvania, School of Medicine, Philadelphia, PA. Her graduate research involved studies of the replication and genetics of avian retroviruses in the laboratory of Dr. David Boettiger. Subsequently, she was a postdoctoral research associate at Harvard Medical School, involved in growth factor research in the laboratory of Dr. Judah Folkman. She joined Chiron as a staff scientist in 1983 to set up the bioassay program. With Drs. Paul Luciw and Dino Dina, she was involved in the cloning of the genome of HIV-1 SF2, one of the first HIV isolates. She led the effort to evaluate recombinant antigens from this isolate for their utility as tools for configuring diagnostic assays to detect HIV-1 infection and as candidate HIV-1 vaccines. Since 1985, she has led the HIV vaccine efforts at Chiron and also is in charge of the laboratory support of evaluation of immune responses of humans enrolled in Phase I, II, and III clinical trials of all of Chiron's viral and bacterial subunit vaccines (HIV-1, HSV, CMV, HPV, influenza, acellular pertussis, etc.), with an emphasis on viral vaccine development. Dr. Steimer has served on several NIH review panels as either an ad hoc or chartered member; is frequently an invited speaker at national and international scientific meetings; has been an active participant at a number of workshops and special conferences assembled by NIAID, WHO, and other scientific bodies; and has published extensively on her scientific work.

Ralph M. Steinman, M.D., is Professor and Senior Physician, Laboratory of Cellular Physiology and Immunology, Director of Rockefeller University M.D./Ph.D. Program, The Rockefeller University. He received his M.D. at Harvard University, Boston, MA., magna cum laude. Prior to his current appointment at The Rockefeller University, Dr. Steinman was a Postdoctoral Fellow, Assistant Professor, and Associate Professor, Laboratory of Cellular Physiology and Immunology, Leukemia Society Scholar, Irma T. Hirschl Fellow, and Established Investigator, American Heart Association. Dr. Steinman has served as ad hoc reviewer for NIAID and has published extensively in peer-reviewed journals, books, and invited reviews on dendritic cells and immunology.

Cladd E. Stevens, M.D., M.P.H., is Head, Laboratory of Epidemiology, New York Blood Center. She received her M.D. from Baylor University College of Medicine, Houston, TX; and her M.P.H. from University of Washington School of Public Health and Community Medicine, Department of Epidemiology and International Health, Seattle, WA. Dr. Stevens carried out hepatitis B vaccine efficacy trials in the late 1970s and 1980s that determined the efficacy of the first recombinant hepatitis B vaccine. She has conducted a large study of the risks and natural history of HIV infection in gay/bisexual men and is currently co-principal investigator for a potential field site for future HIV vaccine efficacy trials. Dr. Stevens is a member of several

professional societies as well as advisory committees and has published over 100 articles in peer-reviewed journals and books.

Peter F. Wright, M.D., is Professor of Medicine, Associate Professor Microbiology & Immunology, and Head, Pediatric Infectious Diseases at Vanderbilt University Medical Center in Nashville, TN. He received a Bachelor of Arts in Biology, Dartmouth College; Masters in Biology, Dartmouth Medical School, Hanover, NH; and a M.D. from Harvard Medical School, Boston, MA. Throughout his career, he has been interested in pediatric vaccines and has led efforts for vaccine evaluation of non-HIV vaccines. Building on this base, an AIDS Vaccine Evaluation Unit was established at Vanderbilt, with Dr. Wright and Dr. Barney Graham as Principle Investigators. Dr. Wright has a special interest in the international application of vaccines and was, until recently, Chairman of the World Health Organization (WHO) Children's Vaccine Initiative Product Development Group on Thermostable Oral Polio vaccine. He is also a member of the Epidemiology and Field Research Steering Group and Chairman of the Measles (ARV)-Poliomyelitis Vaccines Steering Group of WHO. He is the author of many peer-reviewed articles, books, chapters, and invited reviews on pediatric vaccines.